



**Nickel-Catalysed Reductive Aldol Cyclisation:
Scope and Mechanistic Insight**

**Development of Novel Methodologies for the
Silylation and Stannylation of Base-Sensitive
Cyclopropenes**

Thesis Submitted in Accordance with the Requirement of The University
of Edinburgh for the Degree of Doctor of Philosophy

By

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Declaration

I declare that the work contained within this thesis is my own, unless otherwise stated and that it is submitted in accordance with university guidelines.

Signed

Euan Fordyce

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Contents

List of Abbreviations	7
Abstract	10
1. Nickel-Catalysed Reductive and Alkylative Cyclisations	11
1.1 Introduction	11
1.2 Definition	12
1.3 General Mechanistic Considerations	12
1.4 Three-Component Couplings	15
1.4.1 Coupling of Alkenes with Alkynes	15
1.4.2 Coupling of Two Alkynes	21
1.4.3 Coupling of Two Alkenes	23
1.4.4 Coupling of Carbonyl Compounds with Dienes	25
1.4.5 Coupling of Carbonyl Compounds with Allenes	30
1.4.6 Coupling of Carbonyl Compounds with Alkynes	32
1.4.7 Coupling of Alkynes with Epoxides	38
1.5 Combinations and Domino Reactions	40
1.6 Conclusions	42
2. Nickel-Catalysed Reductive Aldol Cyclisations: Scope and Mechanistic Insight	43
2.1 Introduction	43
2.2 Results and Discussion	47
2.2.1 Reaction Optimisation and Scope	47
2.2.2 Mechanistic Considerations	54
2.3 Conclusions	66

2.4 Experimental	67
3. The Chemistry of Cyclopropenes	84
3.1 Introduction	84
3.1.1 Synthesis of Cyclopropenes: An Overview	84
3.1.2 The General Chemistry of Cyclopropenes	89
3.2 Formal Substitution Reactions	93
3.2.1 Cyclopropenes as Electrophilic Species	94
3.2.2 Cyclopropenes as Nucleophilic Species	96
3.3 Conclusions	102
4. Development of Novel Methodologies for the Silylation and Stannylation of Base-Sensitive Cyclopropenes	103
4.1 Introduction	103
4.2 Results and Discussion	109
4.2.1 Direct Silylation of Cyclopropenes	109
4.2.2 Direct Stannylation of Cyclopropenes	114
4.2.3 Applications of Silyl- and Stannylcyclopropenes	118
4.3 Conclusions	124
4.4 Experimental	126
5. References	157

List of Abbreviations

Ac	acetyl
acac	acetylacetonate
aq	aqueous
Ar	aryl
Bn	benzyl
BOC	<i>t</i> -butyloxycarbonyl
br	broad
Bz	benzoyl
cat.	catalyst
cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
d	doublet
dba	dibenzylideneacetone
DIBAL-H	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DOSP	<i>N</i> -(dodecylbenzenesulfonyl)prolinate
dppe	1,2- <i>bis</i> (diphenylphosphino)ethane

DPTI	diphenyltriflylimidazolidinone
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact
EPR	electron paramagnetic resonance spectroscopy
equiv.	equivalent
ES	electrospray
EWG	electron-withdrawing group
FT	Fourier transform
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
IR	infrared spectroscopy
LDA	lithium diisopropylamide
mepy	methyl 2-oxopyrrolidine-5-carboxylate
MEM	β -methoxyethoxymethyl
NHC	<i>N</i> -heterocyclic carbene
NMO	<i>N</i> -methylmorpholine
NMR	nuclear magnetic resonance spectroscopy
OMP	2-methoxyphenyl
pin	pinacol

PMP	4-methoxyphenyl
ppm	parts per million
q	quartet
rt	room temperature
s	singlet
SEM	β -(trimethylsilyl)ethoxymethyl
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	<i>t</i> -butyldimethylsilyl
TES	trimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Ts	tosyl
TTMPP	<i>tris</i> (2,4,6-trimethoxyphenyl)phosphine
UV	ultraviolet spectroscopy

Abstract

I. Nickel-Catalysed Reductive Aldol Cyclisations: Scope and Mechanistic Insight

A highly diastereoselective nickel-catalysed reductive aldol cyclisation is described. Using $\text{Ni}(\text{acac})_2$ as a precatalyst and diethylzinc as a stoichiometric reductant, various α,β -unsaturated carbonyl compounds tethered through an amide or ester linkage to a ketone electrophile underwent efficient cyclisation to afford β -hydroxylactams and β -hydroxylactones respectively. The scope of this process is broad with variation in the α,β -unsaturated carbonyl component, ketone and, where applicable, the nitrogen protecting group all tolerated. A series of experiments, including deuterium-labelling studies, were carried out in an attempt to gain insight into the possible reaction mechanisms that might be operative.

II. Development of Novel Methodologies for the Silylation and Stannylation of Base-Sensitive Cyclopropenes

Two distinct approaches to the synthesis of silyl- and stannylcyclopropenes are described. Using substoichiometric quantities of $\text{Cu}(\text{acac})_2$ and 1,2-*bis*-(diphenylphosphino)ethane in combination with (trifluoromethyl)trimethylsilane, a diverse range of 1,3,3-trisubstituted cyclopropenes underwent direct silylation to afford the corresponding 1-silylcyclopropenes in good to excellent yield. Attempts to adapt these conditions to synthesise the corresponding stannylcyclopropenes proved unsuccessful. However, by employing (pentafluoroethyl)tributylstannane and stoichiometric potassium fluoride, it was possible to access 1-stannylcyclopropenes in comparable yields. It was also demonstrated that both the stannyl- and silylcyclopropene derivatives synthesised using these methodologies were able to serve as precursors for a variety of novel molecules that might otherwise be difficult to access using alternative methods.

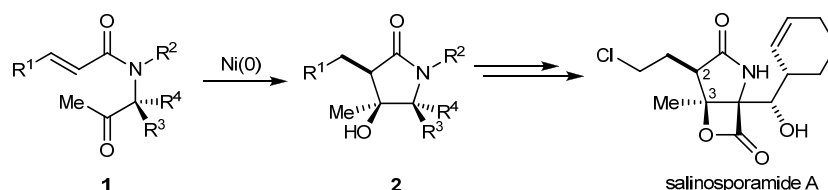
1. Nickel-Catalysed Reductive and Alkylative Cyclisations

1.1 Introduction

The use of transition metals as a means to form new carbon–carbon bonds dates back to the 19th century.¹ In the intervening years, transition metal–catalysed coupling reactions have emerged as one of the most important tools within the organic chemists’ arsenal.

Nickel, in particular, has attracted high levels of interest in recent years because of its use in reductive cyclisations and couplings.² This group of new reactions allows a broad range of multicomponent couplings involving two or more π -components in combination with a stoichiometric reductant. These processes allow the assembly of polyfunctional products, often with high levels of diastereo- and enantiocontrol, from simple achiral, acyclic precursors.

The ability of nickel to facilitate such rapid increases in molecular complexity has attracted the attention of many research groups within the chemical community. Our focus in this area was driven by the desire to develop a novel route to the potent 20S proteasome inhibitor and anti–cancer compound, salinosporamide A (Scheme 1.1).³ This molecule possesses a β -hydroxy- γ -lactam core, which we envisaged could be accessed *via* nickel-mediated cyclisation of the appropriate α,β -unsaturated amide to a tethered methyl ketone, formally a *reductive aldol cyclisation*. We believed that not only would such a transformation give access to the lactam core of salinosporamide A, it would also allow us to install the appropriate stereochemistry at C2 and C3. To this end we initiated a programme targeted at the development of new reductive aldol cyclisations catalysed by nickel (among other metals), with the hope that this could eventually be applied to the synthesis of this interesting and potentially useful natural product.

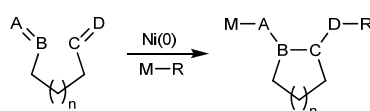


Scheme 1.1 Potential Synthetic Route to Salinosporamide A

In order to place this methodology into context, in this chapter we will present a review of the literature to date on the use of nickel in reductive cyclisations. We will highlight recent discoveries and applications within this rapidly expanding field, while paying particular attention to the mechanistic hypotheses reported.

1.2 Definition

Before we examine the literature on nickel-catalysed reductive cyclisations we must first define the parameters of the reaction. In a reductive cyclisation, two π -systems are combined with a reducing agent to form a new carbon–carbon bond (Scheme 1.2). As a consequence of the coupling event the two π -systems undergo a net two-electron reduction, while the reducing agent undergoes a net two-electron oxidation.

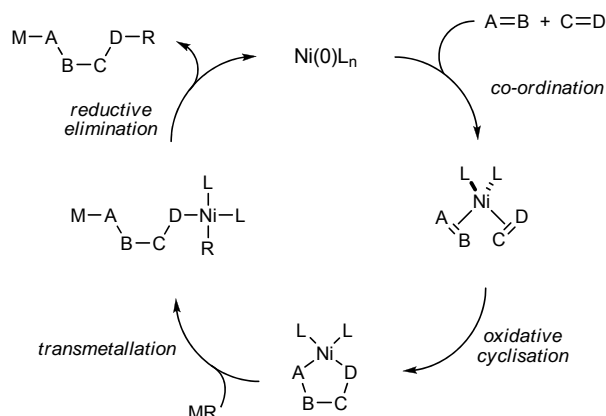


Scheme 1.2 Reductive Cyclisation of Two π -Components

1.3 General Mechanistic Considerations

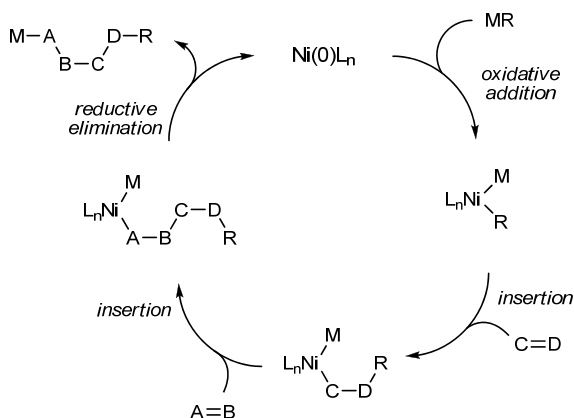
Many examples of nickel-catalysed reductive cyclisations have been reported over the years and in most cases the authors have proposed mechanisms to explain their transformations. Although numerous, these mechanism can be categorised into three

main types, which differ in terms of the oxidative transformation that initiates the catalytic cycle. The first, and most frequently used, involves oxidative cyclisation of Ni(0) with the two π -components to form a metallacycle (Scheme 1.3). Subsequent transmetalation with the organometallic reagent MR and reductive elimination then provides the desired product, while regenerating Ni(0) to complete the catalytic cycle.



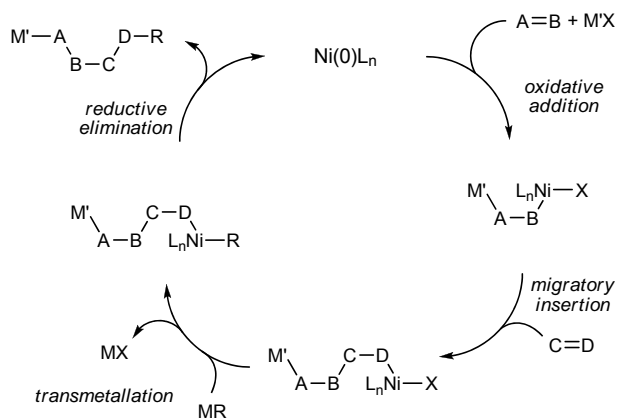
Scheme 1.3 Possible Mechanistic Pathway Initiated by Oxidative Cyclisation of Two π -Components with Ni(0)

Alternatively these reactions can be initiated by oxidative addition of Ni(0) to the organometallic reagent MR (Scheme 1.4). The resulting nickel hydride or alkyl nickel then undergoes sequential insertions into C=D and A=B before undergoing reductive elimination to generate the product.



Scheme 1.4 Possible Mechanistic Pathway Initiated by Oxidative Addition of Ni(0) to the Reducing Agent

The final type of catalytic cycle is initiated by Lewis acid (M'X)–mediated oxidative addition of Ni(0) to one of the π –components (Scheme 1.5). Migratory insertion into the second π –component, transmetallation of MR and then reductive elimination affords the desired product.



Scheme 1.5 Possible Mechanistic Pathway Initiated by Oxidative Addition of Ni(0) to one of the π -Components

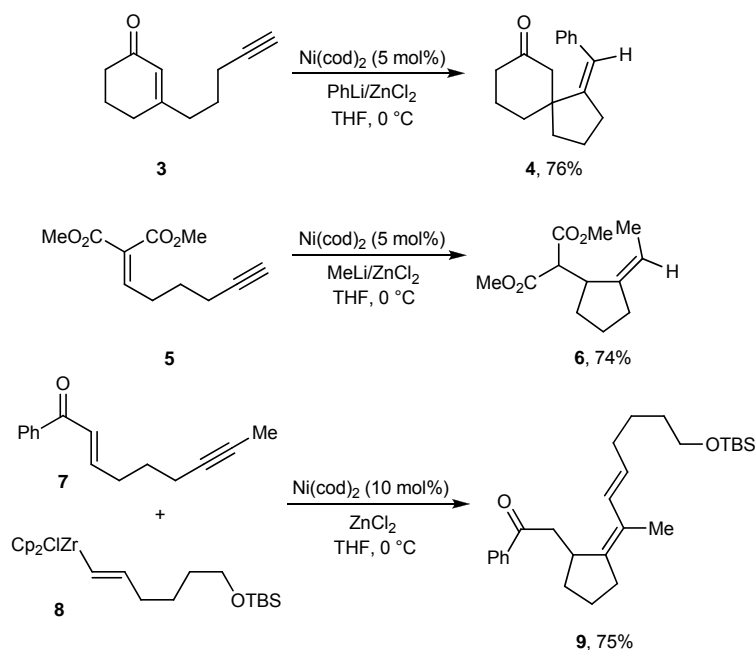
These are undoubtedly oversimplified descriptions, and many variations of the three mechanism classes summarised are possible. Issues such as metal coordination number, prior association of reactive components, and changes in the hapticity of

unsaturated reactive ligands provide many reasonable variations in the mechanisms highlighted above. Furthermore, electron-transfer processes are certainly possible and have been well documented in other classes of Ni(0)-catalysed reactions.⁴ The involvement of electron-transfer pathways could be important in the individual steps of the three mechanism classes illustrated above.

1.4 Three-Component Couplings

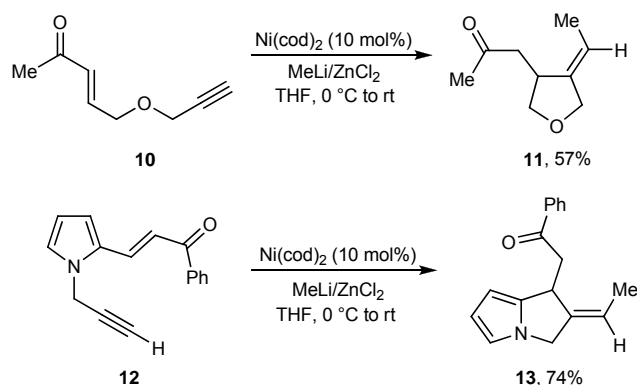
1.4.1 Coupling of Alkenes with Alkynes

The nickel-catalysed reductive cyclisation of enynes has been demonstrated to be a highly flexible method for the stereoselective synthesis of exocyclic tri- and tetrasubstituted alkenes. The earliest example of this type of reductive cyclisation was reported by Montgomery and co-workers in 1996.^{5a} In this study, and in subsequent reports from this group, a variety of electron-deficient alkenes were coupled with both terminal and internal alkynes using organozinc,⁵ organoaluminium⁶ and alkenyl zirconium reagents⁷ as stoichiometric reductants (Scheme 1.6). The resulting carbocycles were obtained in good to excellent yield and with a high degree of stereoselectivity.



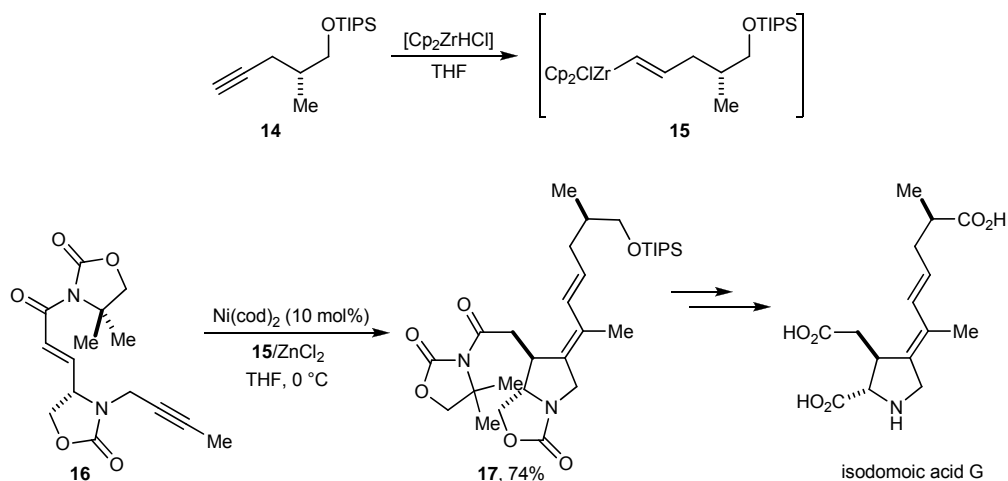
Scheme 1.6 Examples of the Cyclisation of Enynes

Substrates containing heteroatoms such as oxygen and nitrogen within the tether between the alkene and alkyne can also be cyclised to yield a variety of interesting heterocyclic rings (Scheme 1.7).^{5c}



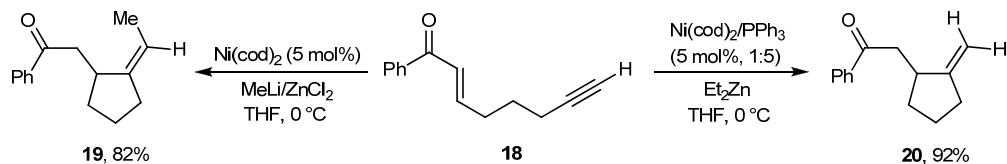
Scheme 1.7 Examples of the Synthesis of Heterocyclic Rings by Enyne Cyclisation

This property was used by Montgomery and co-workers in the synthesis of isodomoic acid G, a member of the kainoid amino acid family of naturally occurring molecules.⁸ The nickel-catalysed cyclisation of alkyne **16** with the vinyl zirconium reagent **15**, generated from alkyne **14**, was used to prepare the isodomoic acid G core structure (Scheme 1.8). In one step, the pyrrolidine unit, the C2/C3 relative stereochemistries, and the complete densely functionalised 1,3-diene were assembled in an efficient and selective fashion.



Scheme 1.8 Key Step in the Total Synthesis of Isodomoic Acid G

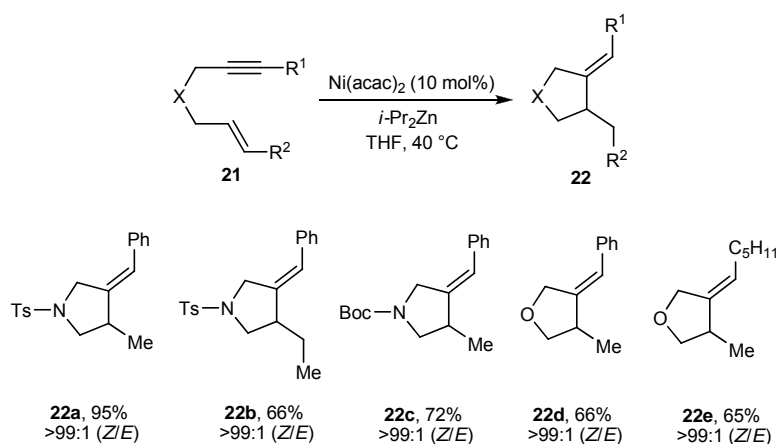
It was noted during these studies that reactions involving organozinc reagents that bear β -hydrogen atoms are sensitive to ligand effects.⁵ In the absence of phosphine ligand, alkylative cyclisation is observed, whereby an alkyl group is incorporated into the cyclised product (**19**, Scheme 1.9). However, pretreatment of the nickel(0) catalyst with triphenylphosphine results in selective hydrogen atom incorporation and hence reductive cyclisation (**20**, Scheme 1.9).



Scheme 1.9 Effect of Phosphane Additives on the Reactivity of Organozinc Reagents that bear β -Hydrogen Atoms

In all the examples reported thus far, electron-deficient alkenes are required for the reaction to be successful. However, this requirement has recently been overcome with the report by Lei and co-workers of a nickel-catalysed reductive cyclisation of unactivated 1,6-enynes.⁹ Using optimised conditions it was demonstrated that a variety of nitrogen- and oxygen-tethered enynes were cyclised in good to excellent

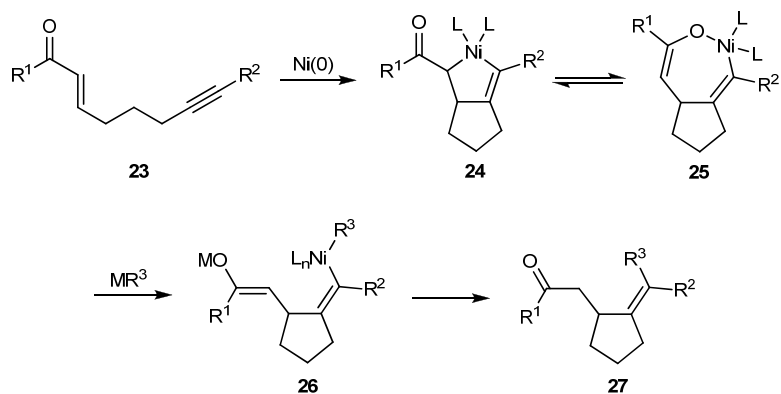
yield and with exceedingly high selectivity for the *Z*-configured alkene (Scheme 1.10). The reaction was demonstrated to be tolerant of both alkyl and aromatic substituents on the alkyne, as well as internal and terminal alkenes and, in the case of the nitrogen tethered enynes, variation of the nitrogen protecting group.



Scheme 1.10 Enyne Cyclisation using Unactivated Alkenes

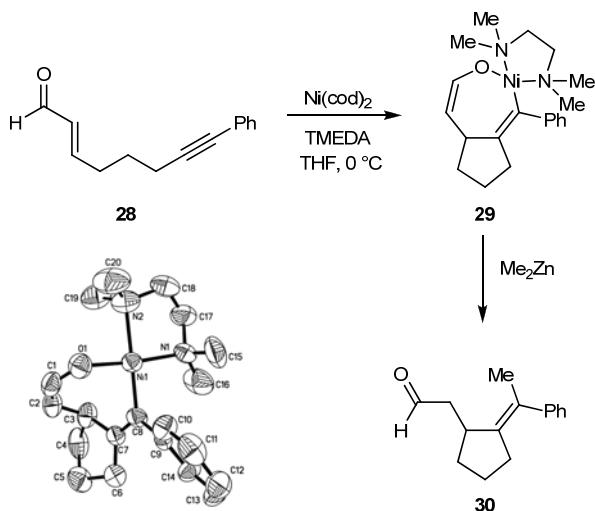
From a mechanistic perspective, both Montgomery⁵ and Lei⁹ have proposed that these transformations involve initial formation of a metallacycle *via* oxidative cyclisation of the two π -components (Scheme 1.11).^{*} Subsequent transmetalation of the main-group organometallic reagent and reductive elimination then provides the desired product.

^{*} Illustrated in Scheme 1.11 is the metallacycle that would form on oxidative cyclisation of an activated enyne. Related metallacycles would be formed with unactivated enynes.



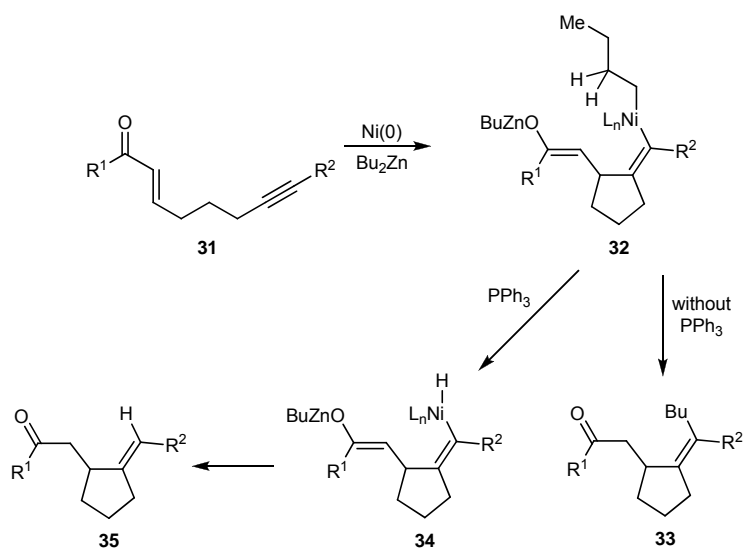
Scheme 1.11 Proposed Mechanism for Enyne Cyclisation

Montgomery and co-workers have provided evidence to support this mechanistic pathway by exposing enyne **28** to stoichiometric quantities of Ni(cod)_2 and TMEDA, in the absence of stoichiometric reductant (Scheme 1.12).¹⁰ Metallacycle **29** was isolated and fully characterised as the η^1 , oxygen-bound enolate. Treatment of metallacycle **29** with stoichiometric dimethylzinc afforded the same product, **30**, which may be obtained from the catalytic reaction of alkynyl enal and dimethylzinc. Although this observation does not prove that catalytic reactions proceed by this mechanism, it does support one of the key steps.



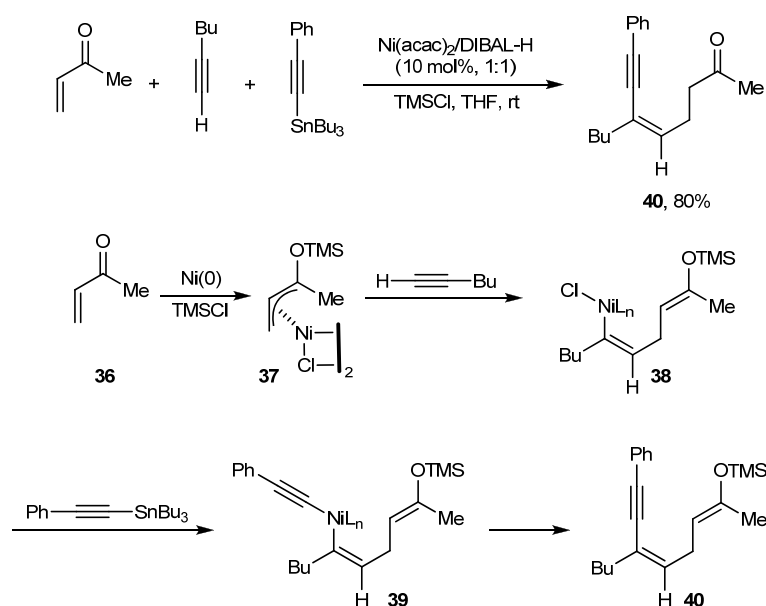
Scheme 1.12 Enyne Cyclisation in the Absence of Reducing Agent

Montgomery and co-workers have used this mechanism to explain the ligand effects observed in their intramolecular cyclisations using β -hydrogen containing organozinc reagents.^{5a,b} They have proposed that the σ -donating ability of the phosphine ligands increases the electron density on nickel in intermediate **32**, hence favouring β -hydride elimination over reductive elimination (Scheme 1.13).



Scheme 1.13 Ligand Dependence of Enyne Cyclisation

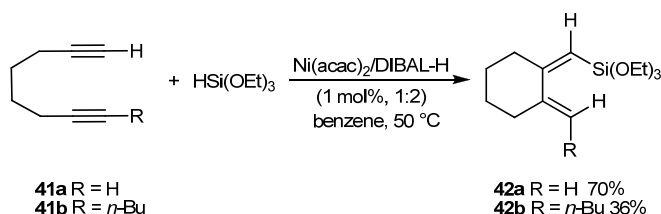
Alternative mechanisms for the coupling of alkenes and alkynes have been proposed. For example, in related intermolecular couplings of enones Ikeda suggested that the reaction proceeds *via* Lewis acid-promoted oxidative addition of nickel(0) to the enone to yield a π -allyl intermediate (**37**, Scheme 1.14).^{11,12} Alkyne insertion, transmetalation of the organometallic reagent, and reductive elimination would afford the desired product. Since TMSCl is not a required additive in all alkene/alkyne couplings, the metallacycle-based mechanism is probably more reasonable based on current available data.



Scheme 1.14 Alternative Mechanism for Enyne Cyclisation

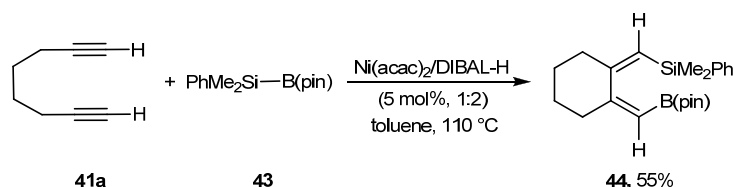
1.4.2 Coupling of Two Alkynes

In 1989 Tamao, Ito and co-workers reported the first examples of the nickel-catalysed reductive cyclisation of two alkynes.¹³ During these studies it was demonstrated that 1,7-diynes cyclisation cleanly to produce six-membered ring products with a *Z*-configured vinyl silane moiety (Scheme 1.15). Both terminal and mixed terminal/internal alkynes were tolerated, with the silyl unit chemoselectively introduced at the terminal alkyne. Although terminal alkynes generally provided the product in high yield, yields obtained with tethered internal alkynes were much lower.



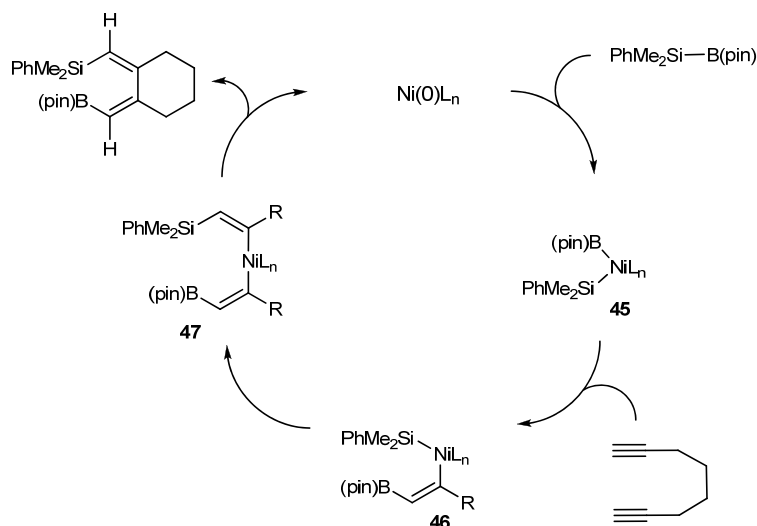
Scheme 1.15 Examples of the Reductive Cyclisations of 1,7-Diynes

Ito and co-workers have demonstrated that variation in the reductant is also possible, with silylboranes being used to yield potentially useful 1-silyl-4-boryl-1,3-dienes.¹⁴ Using silylboranes **43** as a reductant 1,7-octadiyne was cyclised to yield the desired dimethylenecyclohexane derivative **44** in 55% yield (Scheme 1.16). Related germaborations using germylboranes were also successful.



Scheme 1.16 Example of the Reductive Cyclisation of 1,7-Octadiyne Using a Silylborane as a Stoichiometric Reductant

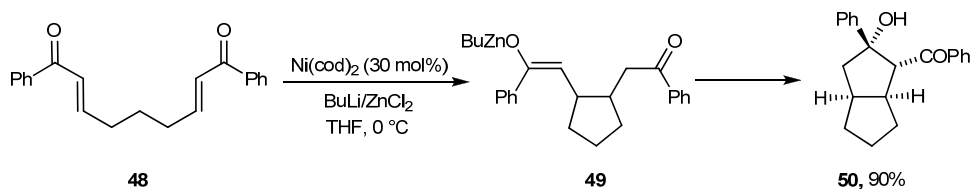
Both Tamao¹³ and Ito¹⁴ proposed mechanisms that involve initial oxidative addition of the Si-H, Si-B or Ge-B bond to nickel(0) to generate intermediates such as **45** (Scheme 1.17). Ito proposed that with silylboranes, subsequent insertion of one alkyne into the Ni-B bond and then a second alkyne into the Ni-Si bond would afford the divinyl nickel species **47**.¹⁴ Direct reductive elimination of this species affords the desired product. The analogous mechanism involving insertion of the second alkyne into the initially formed vinyl nickel species was deemed unlikely in intermolecular couplings on the basis of regiochemical considerations.



Scheme 1.17 Proposed Mechanism for the Reductive Cyclisation of 1,7-Diynes

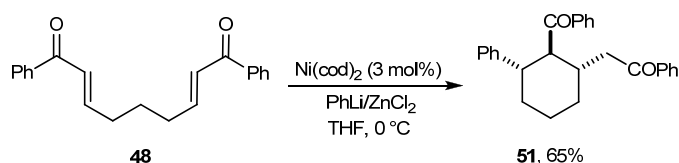
1.4.3 Coupling of Two Alkenes

Although a great deal of research has focused on the use of alkynes in coupling reactions, very little progress has been made in the corresponding nickel-catalysed reductive coupling of two alkenes. Savchenko and Montgomery have studied the cyclisation of *bis*-enones using $\text{Ni}(\text{cod})_2$ and organozinc reagents as reductants.^{5b,15} It was reported that this type of cyclisation is highly dependent on the structure of the organozinc reductant. Cyclisation with sp^3 -hybridised organozinc reagents such as dibutylzinc affords [3.3.0] bicyclooctanol products efficiently *via* reductive cyclisation followed by aldol addition of the resulting ketoenolate (Scheme 1.18). High *cis* selectivities of the cyclopentyl substituents were typically observed.



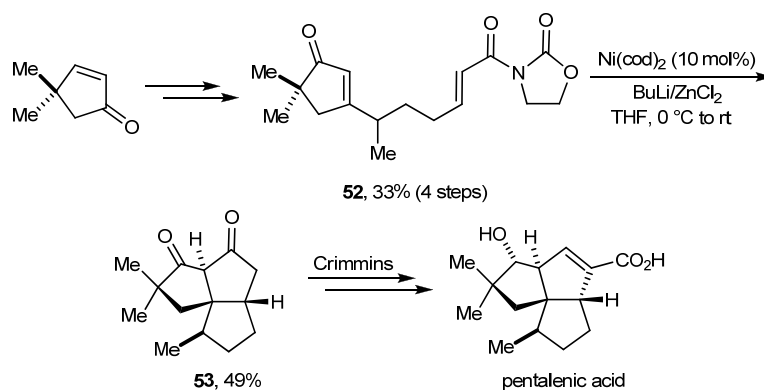
Scheme 1.18 The Reductive Cyclisation of a *bis*-Enone using a sp^3 -Hybridised Organozinc Reagent

However, use of the more reactive sp^2 -hybridised organozinc reagent, diphenylzinc, resulted in the efficient production of the trisubstituted cyclohexane **51** (Scheme 1.19) as a single diastereomer in 65% yield by a mechanism involving two sequential conjugate additions.



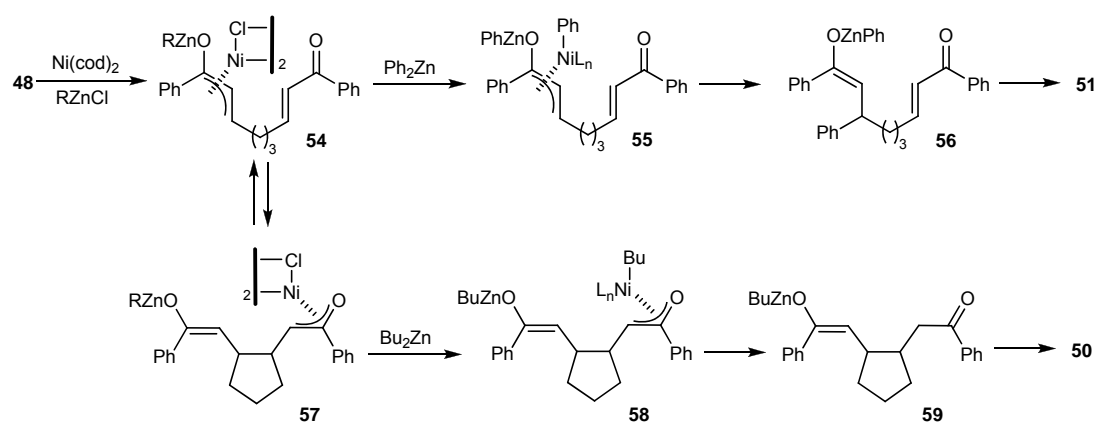
Scheme 1.19 The Reductive Cyclisation of *bis*-Enones using sp^2 -Hybridised Organozinc Reagents

Montgomery and co-workers used this methodology in the formal synthesis of pentalenene, pentalenic acid, and deoxypentalenic acid.¹⁶ Exposure of *bis*-enone **52**, prepared in four steps from dimethylcyclopentenone, to $BuLi/ZnCl_2$ and $Ni(cod)_2$ afforded triquinane **53** in 49% yield as a mixture of epimers (Scheme 1.20). Compound **53** had previously been converted into each of the triquinane natural products noted above.¹⁷



Scheme 1.20 Triquinane Synthesis through Nickel-Catalysed *bis*-Enone Cyclisation

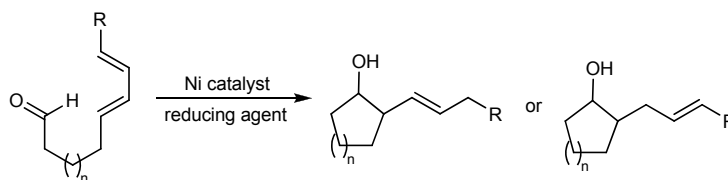
Although little is known about the mechanisms of these interesting coupling reactions Montgomery suggests that *bis*-enone cyclisations may be initiated by oxidative addition of nickel(0) to one of the enones yielding π -allyl complex **54** (Scheme 1.21).¹⁵ Transmetalation of an sp^2 -hybridised organozinc reagent followed by reductive elimination would afford zinc enolate **56** which would cyclise to produce **51**. Alternatively, if transmetalation of an sp^3 -hybridized organozinc is slower, as is the case in most cross-coupling reactions, migratory insertion to produce nickel enolate **57** could occur. Nickel enolate **57** could then be converted to keto enolate **59** either by a β -hydride elimination/reductive elimination sequence or by conversion to a *bis*-zinc enolate followed by monoprotection on workup. Intramolecular aldol addition would then afford the observed products. However, this does not rule out the possibility of metallacycle based mechanisms.



Scheme 1.21 Proposed Mechanism for *bis*-Enone Cyclisation

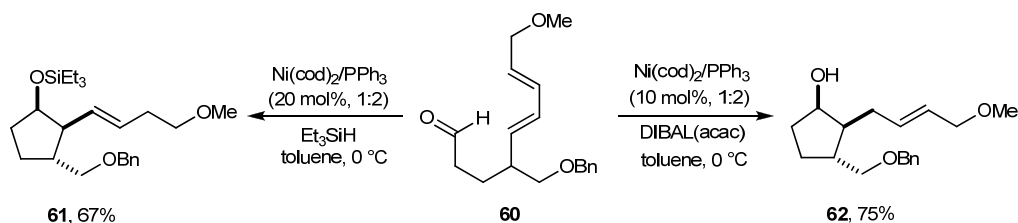
1.4.4 Coupling of Carbonyl Compounds with Dienes

The nickel-catalysed reductive cyclisation of a 1,3-diene to a tethered carbonyl group may proceed in either the 1,4- or 1,2- sense to afford either homoallylic or *bis*-homoallylic alcohols (Scheme 1.22).



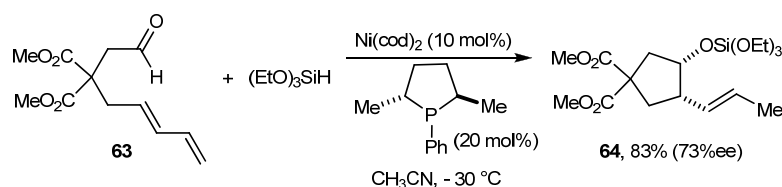
Scheme 1.22 Reductive Cyclisation of Aldehydes with 1,3-Dienes

Mori and co-workers have demonstrated that the selectivity for formation of either homoallylic alcohol or *bis*-homoallylic alcohol can be controlled by variation of the reducing agent (Scheme 1.23).¹⁸ For example, exposure of 1,3-diene **60** to $\text{Ni}(\text{cod})_2/\text{PPh}_3$ in the presence of triethylsilane afforded the homoallylic alcohol **61** as the sole product in 67% yield. Alternatively, exposure of the same substrate to $\text{Ni}(\text{cod})_2/\text{PPh}_3$ in the presence of DIBAL(acac) yielded the *bis*-homoallylic alcohol **62** in 75% yield.



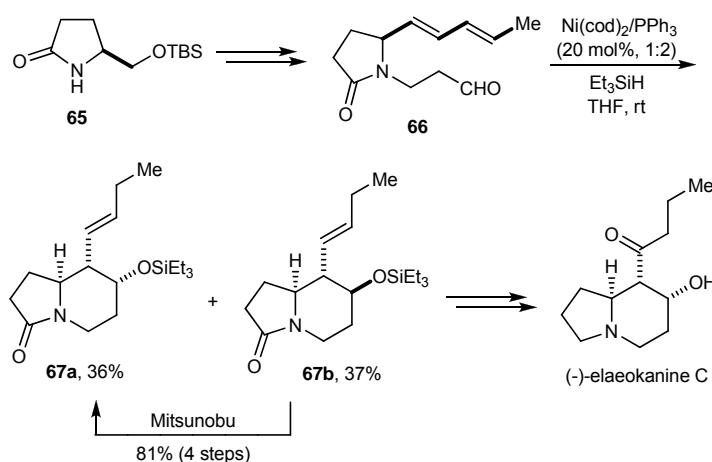
Scheme 1.23 Selective Cyclisation through Variation of the Reducing Agent

By replacing triphenylphosphine with a chiral monodentate phosphine ligand, (2*R*, 5*R*)-2,5-dimethyl-1-phenylphospholane, Mori and co-workers have been able to make this process asymmetric, yielding the desired cyclopentanol derivative **64** in excellent yield and with modest enantioselectivity (Scheme 1.24).¹⁹



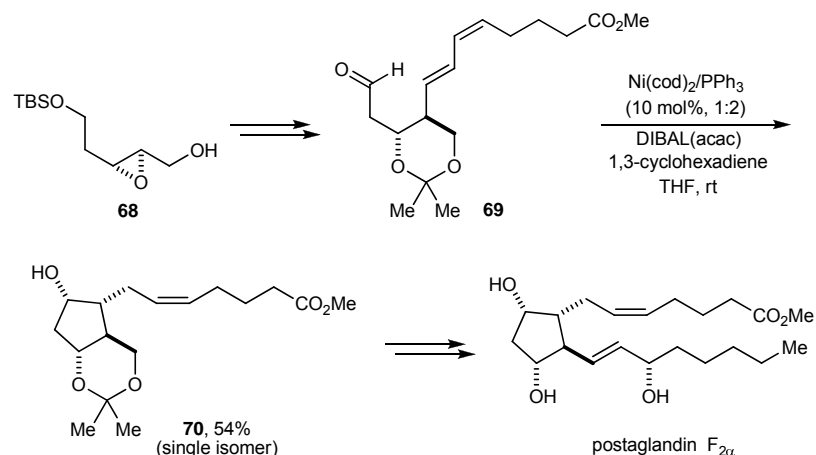
Scheme 1.24 Asymmetric Variant of the Intramolecular Coupling of Aldehydes with Dienes

This ability to control the reaction outcome through variation in the reductant has been used to synthesise two very different natural products. In the synthesis of indolizidine alkaloid (-)-elaeokanine C, Mori and co-workers treated cyclisation precursor **66** with catalytic quantities of $\text{Ni}(\text{cod})_2/\text{PPh}_3$ in the presence of triethylsilane to afford homoallylic products **67a** and **67b** in 73% yield as a 1:1 mixture of diastereomers (Scheme 1.25).²⁰ Although a mixture of diastereomers was obtained, the undesired isomer **67b** was recycled by a Mitsunobu reaction to **67a**, which was then converted into an advanced intermediate, thus completing the formal synthesis of elaeokanine C.



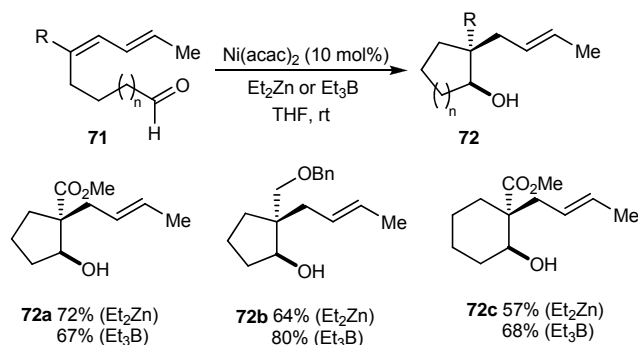
Scheme 1.25 Total Synthesis of (-)-Elaeokanine C through Nickel-Catalysed Aldehyde-Diene Cyclisation

In the total synthesis of prostaglandin $\text{F}_{2\alpha}$, Mori and co-workers cyclised complex 1,3-diene **69** in the presence of $\text{Ni}(\text{cod})_2/\text{PPh}_3$ and 1,3-cyclohexadiene, using DIBAL(acac) as a stoichiometric reductant, to yield the desired *bis*-homoallylic alcohol **70**, with complete control of the contiguous stereocentres and alkene stereochemistry (Scheme 1.26).²¹ Compound **70** was then converted into prostaglandin $\text{F}_{2\alpha}$ in a straightforward fashion to complete a very attractive synthesis of this natural product.



Scheme 1.26 Total Synthesis of Prostaglandin $F_{2\alpha}$ through Nickel-Catalysed Aldehyde-Diene Cyclisation

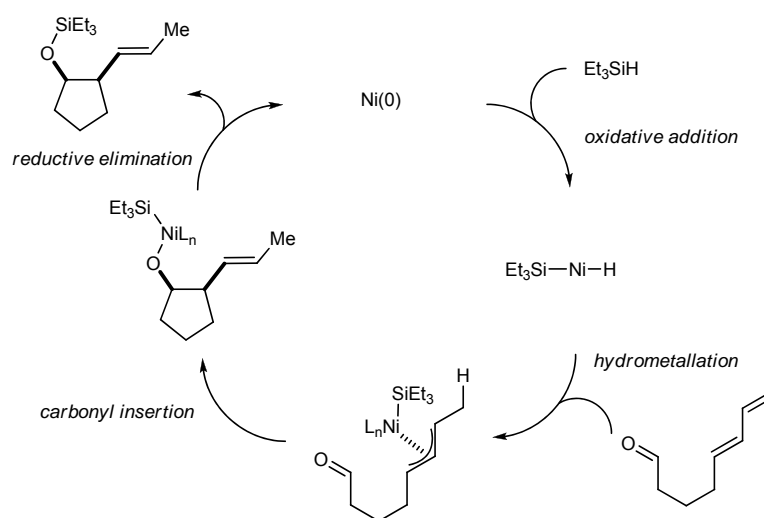
Tamaru and co-workers have demonstrated that it is also possible to use organozinc and organoborane reagents as stoichiometric reductants in the nickel-catalysed reductive cyclisation of 1,3-dienes tethered to aldehydes.²² Using diethylzinc or triethylborane, a variety of ω -dienyl aldehydes were cyclised to yield the corresponding *bis*-homoallylic alcohols in good yield and with high stereoselectivity (Scheme 1.27).



Scheme 1.27 Examples of Nickel-Catalysed Cyclisations of ω -Dienyl Aldehydes using Organozinc and Organoborane Reducing Agents[†]

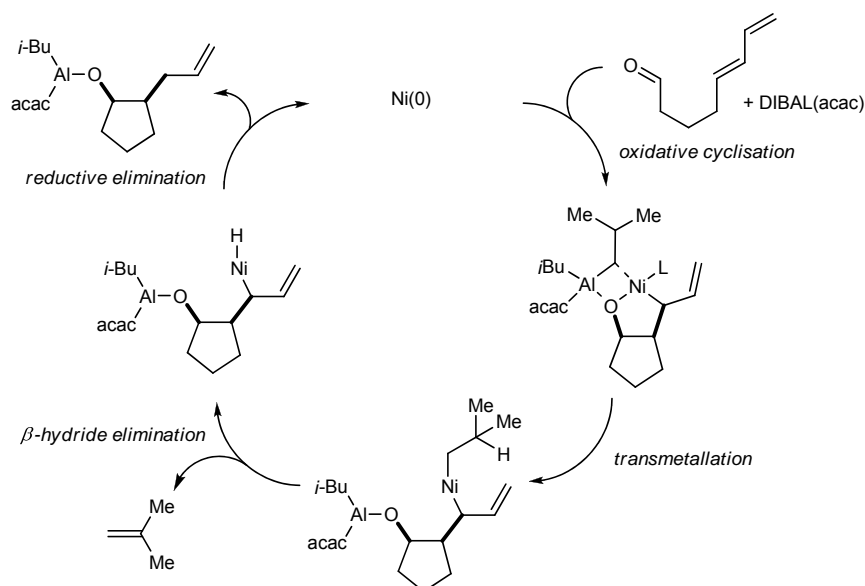
[†] It should be noted, however, that the lower yields obtained for **72b** and **72c** were due to formation of by-products arising from 1,2-addition of Et_2Zn to the tethered aldehyde.

Mori proposed that two different mechanisms are in operation in the reductive cyclisation of diene aldehydes.^{18d} When triethylsilane is used, it is believed that the reaction is initiated by oxidative addition of nickel(0) to the silane (Scheme 1.28). Hydrometallation of the diene gives a π -allyl intermediate, which subsequently undergoes carbonyl insertion and reductive elimination to afford the desired homoallylic alcohol derivative.



Scheme 1.28 Possible Mechanism that Explains Formation of Homoallylic Alcohol Derivatives

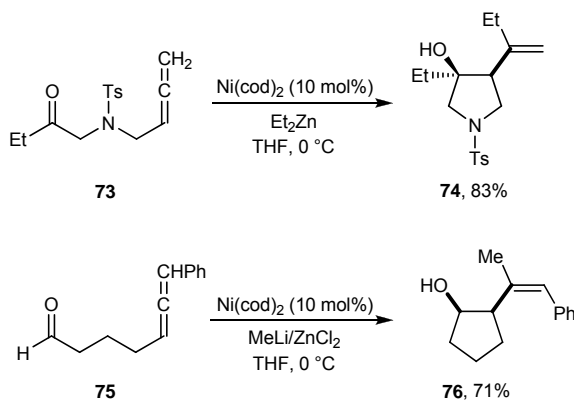
Alternatively, when DIBAL(acac) is used as a reducing agent, it is believed that the reaction is initiated by oxidative cyclisation of the 1,3-diene and aldehyde to afford a metallacycle (Scheme 1.29). Subsequent transmetallation, β -hydride elimination and reductive elimination could explain the synthetic outcome of these reactions. A similar mechanism was proposed by Tamaru and co-workers for the organozinc and organoborane-mediated cyclisations.



Scheme 1.29 Possible Mechanism that Explains Formation of *bis*-Homoallylic Alcohol Derivatives

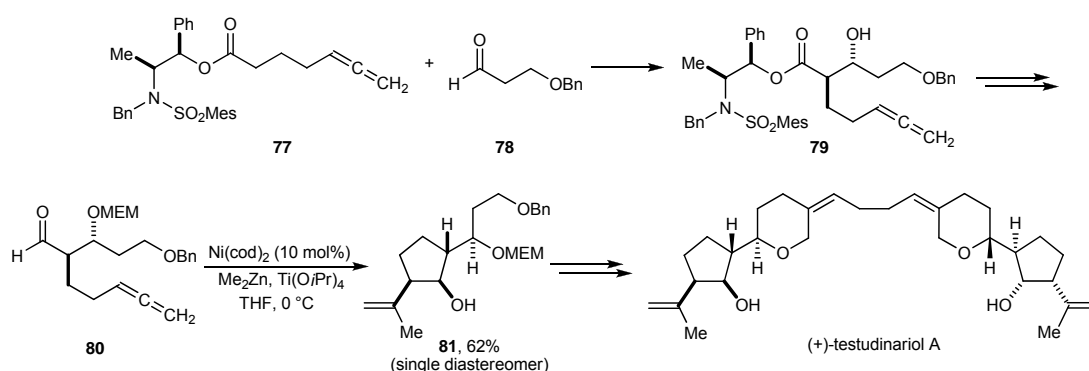
1.4.5 Coupling of Carbonyl Compounds with Allenes

The alkylative cyclisation of allenyl aldehydes has been developed as an efficient method to prepare homoallylic alcohols. Both Kang and Yoon²³ and Montgomery and Song²⁴ have demonstrated that allenyl aldehydes and ketones undergo efficient cyclisation in the presence of either a commercial organozinc reagent or an organozinc reagent, generated *in situ* from the requisite organolithium and zinc chloride, to yield the corresponding *N*-tosyl pyrrolidines or 5-membered carbocycles (Scheme 1.30). In most cases high *cis*-selectivities were observed and where 1,3-disubstituted allenes were used high *Z*-selectivities were typically observed.



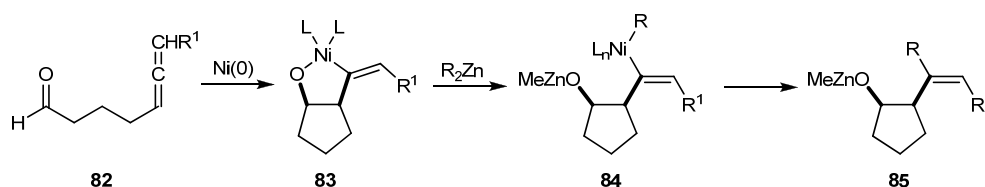
Scheme 1.30 Cyclisation through Coupling of Aldehydes and Ketones with Monosubstituted and 1,3-Disubstituted Allene Groups

Montgomery and co-workers have used a nickel-catalysed aldehyde/allene cyclisation in the total synthesis of (+)-testudinariol A, a member of a small family of C_2 -symmetric natural products with an internal butylene core (Scheme 1.31).²⁵ The synthesis began with an Abiko-Masamune asymmetric anti aldol reaction²⁶ to assemble compound **79**, which was converted into the cyclisation precursor **80**. Treatment of **80** with dimethylzinc and catalytic $\text{Ni(cod)}_2/\text{PBU}_3$, with Ti(Oi-Pr)_4 as a coadditive, resulted in the selective production of **81** as a single diastereomer in 62% yield. Compound **81** was subsequently transformed into (+)-testudinariol A in three steps.



Scheme 1.31 Total Synthesis of (+)-Testudinariol through Nickel-Catalysed Aldehyde-Allene Cyclisation

The mechanism for alkylative cyclisations is thought to involve oxidative cyclisation of the two π -components with Ni(0) to form nickel metallacycle **83** (Scheme 1.32).^{23,24} Transmetalation of the organozinc reagent, followed by reductive elimination would afford the observed products. However, alternative pathways involving carbonickelation or nickel-catalysed carbozincation cannot be excluded.

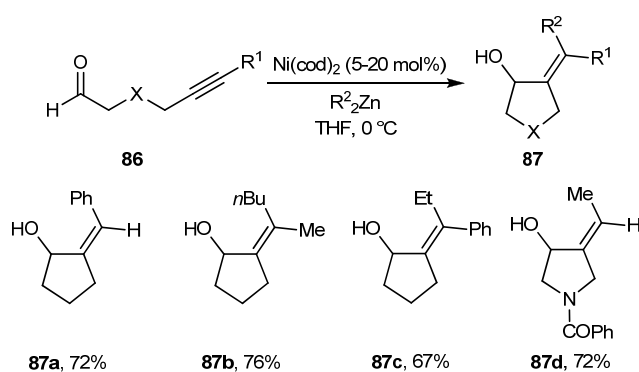


Scheme 1.32 Possible Mechanism for Nickel-Catalysed Cyclisation of Allenyl Aldehydes

1.4.6 Coupling of Carbonyl Compounds with Alkynes

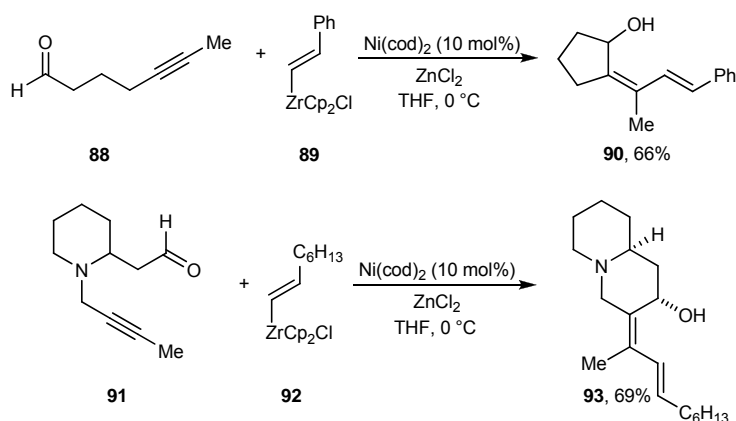
The nickel-catalysed cyclisation of ynals has been extensively developed in both reductive and alkylative processes in recent years and is still a very active field. This type of coupling gives rise to structurally diverse and synthetically useful allylic alcohols.

Montgomery and co-workers reported the first examples of nickel-catalysed alkylative cyclisations of ynals in 1997.²⁷ It was demonstrated that a diverse range of ynals could be efficiently cyclised with stereoselective formation of the exocyclic tri- or tetrasubstituted alkene (Scheme 1.33). Both sp²- and sp³-hybridised organozinc reagents, including those that possess β -hydrogens, were efficiently incorporated without competing β -hydride elimination



Scheme 1.33 Examples of Nickel-Catalysed Alkylative Cyclisations of Ynals

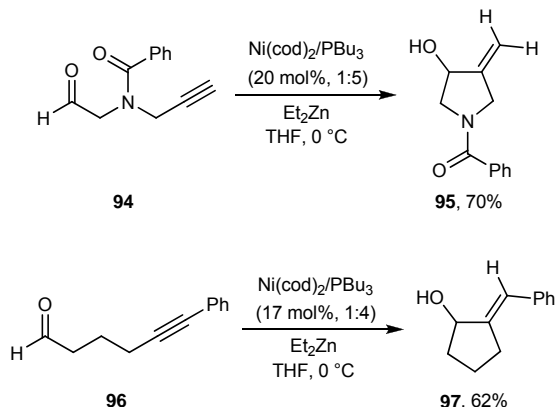
Problems were encountered, however, when attempting alkylative cyclisations using alkenyl zinc reagents, with undesired 1,2-addition to the aldehyde being observed. This problem was solved through the use of alkenyl zirconium reagents (Scheme 1.34).⁷



Scheme 1.34 Examples of the Alkylative Cyclisation of Ynals using Alkenyl Zirconium Reagents

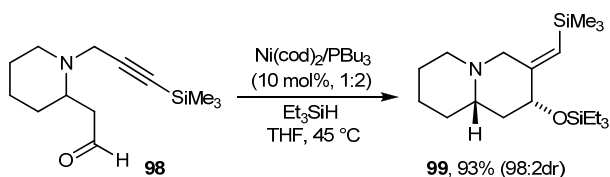
Although competing β -hydride elimination was not observed in the cyclisations involving diethylzinc or dibutylzinc, a complete crossover to reductive cyclisation with hydrogen-atom introduction was observed simply by pretreating the nickel-catalyst with tributylphosphine (Scheme 1.35).²⁷ Reductive cyclisations were efficient with both terminal and internal alkynes, with the latter allowing completely

selective introduction of trisubstituted alkenes of the opposite configuration as those obtained from alkylative cyclisations of terminal alkynes (compare **97**, Scheme 1.35 with **87a**, Scheme 1.33).



Scheme 1.35 Examples of Nickel-Catalysed Reductive Cyclisation of Ynals

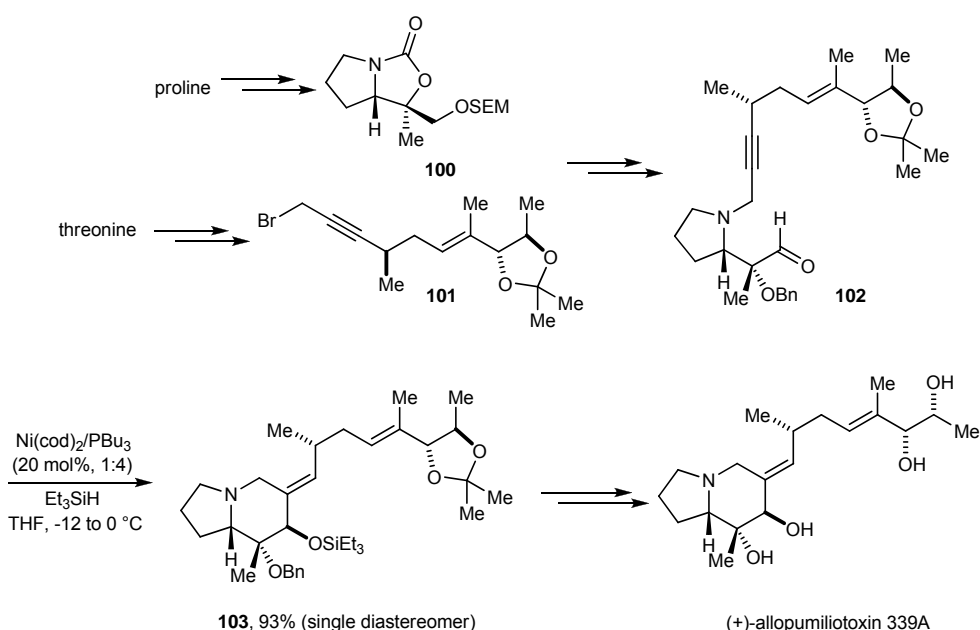
Although diethylzinc has been demonstrated to serve as an effective reductant in the reductive cyclisation of simple ynals, problems were encountered when more complex substrates were used. In such cases, selectivity between hydrogen atom and ethyl group incorporation is reduced, and direct 1,2-addition of diethylzinc to the aldehyde is observed. Montgomery and co-workers overcame these problems by employing triethylsilane as a reducing agent (Scheme 1.36).²⁸



Scheme 1.36 Reductive Cyclisation of an Ynal using Triethylsilane as the Reducing Agent

Tang and Montgomery have used these conditions to complete the total synthesis of three members of the pumiliotoxin family of natural products.²⁸ In a representative

example, (+)-allopumiliotoxin 339A was prepared from structurally complex ynal **102**, which was assembled from proline and threonine (Scheme 1.37). Cyclisation of ynal **102** with triethylsilane and a substoichiometric quantity of $\text{Ni}(\text{cod})_2/\text{PBU}_3$ afforded bicycle **103** as a single diastereomer in 93% yield. This single step assembles the six-membered ring of the indolizidine core, controls the relative stereochemistry adjacent to a quaternary centre, and assembles the alkylidene unit, with each of these features being controlled in a completely selective manner. Simple deprotection of the nickel-mediated cyclisation product allowed completion of the synthesis.



Scheme 1.37 Total Synthesis of (+)-Allopumiliotoxin 339A through Nickel-Catalysed Ynal Cyclisation

By replacing the tributylphosphine ligands with *N*-heterocyclic carbene (NHC) ligand **104** (Figure 1.1),²⁹ Montgomery and co-workers have reported the first examples of nickel-catalysed macrocyclisations of ynals containing terminal alkynes.³⁰ Under optimised conditions a variety of ynals were cyclised to generate macrocycles varying in size ranging from 14- to 22-membered rings (Scheme 1.38). In all cases only the endocyclic *E*-olefins were observed.

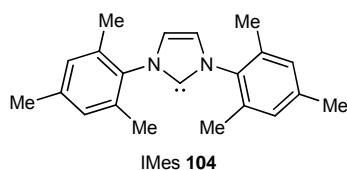
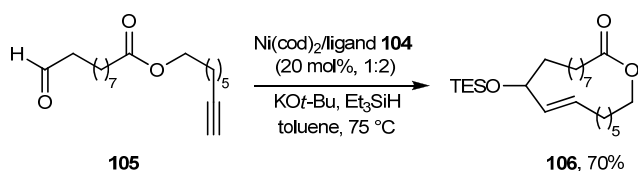
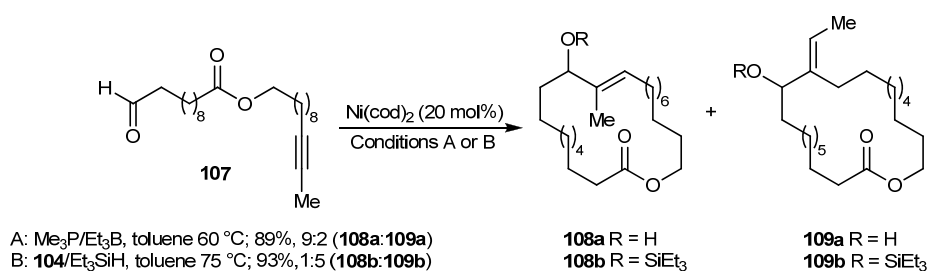


Figure 1.1



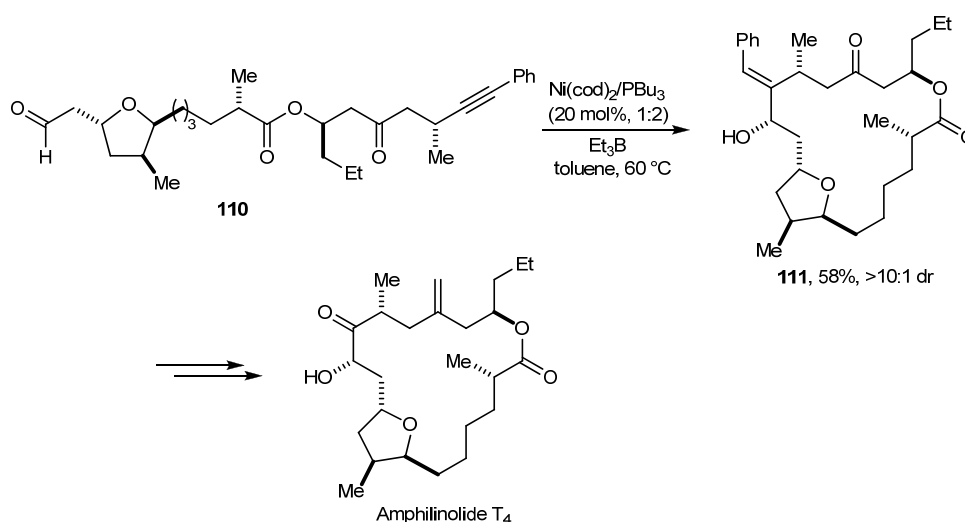
Scheme 1.38 Nickel-Catalysed Macrocyclisation

Montgomery and co-workers also reported that the corresponding macrocyclisations of ynals containing internal alkynes were both substrate and ligand dependent.³⁰ It was described that while phenyl-substituted ynals cyclise to produce only exocyclic products, the corresponding cyclisations of aliphatic internal alkynes produced varying mixtures of both exo- and endocyclic products depending on the ligand used (Scheme 1.39). The addition of the bulkier carbene **104** afforded the exocyclic olefin as the major product in a 5:1 ratio, whereas the endocyclic product was favoured when using trimethylphosphine in combination with triethylborane.



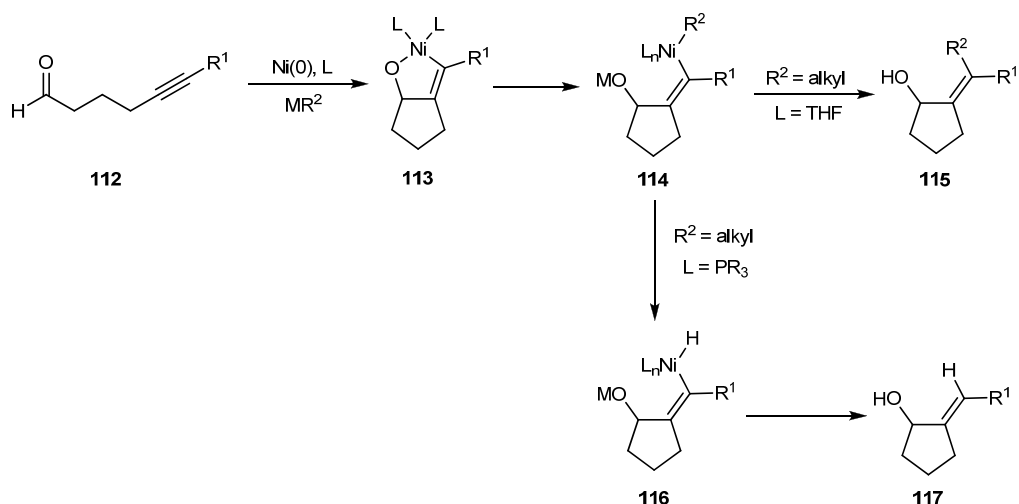
Scheme 1.39 Nickel-Catalysed Macrocyclisation of an Ynal that contains an Aliphatic Internal Alkyne

By using the allylic alcohols formed in these nickel-catalysed reductive macrocyclisations as masked α -hydroxy ketones, Jamison and co-workers have applied conditions they developed for the intermolecular coupling of aldehydes and alkynes³¹ to complete the total synthesis of amphidinolides T1 and T4 (Synthesis of amphidinolide T4 is illustrated in Scheme 1.40).³² In both natural products, the macrocyclisation proceeded with excellent regioselectivity and diastereoselectivity. Protection of the allylic alcohol followed by ozonolysis, selective methylenation and HF deprotection afforded the respective amphidinolides.



Scheme 1.40 Total Synthesis of Amphidinolide T4 through Nickel-Catalysed Macrocyclisation of an Ynal

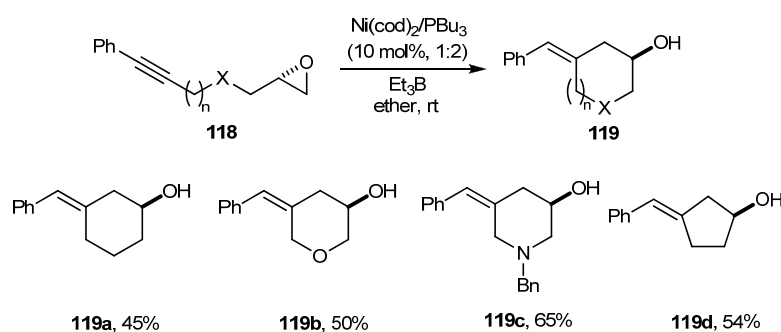
It has been proposed that these transformations involve oxidative coupling of the alkyne and aldehyde with nickel(0) to afford oxametallacycle **113**, followed by a transmetallation/reductive elimination sequence (Scheme 1.41).^{27a} The initial oxidative cyclisation is promoted by the reducing agent and the structure of the ligand, substrate and reducing agent all play a role in controlling the β -hydride elimination/reductive elimination selectivity. In addition to the oxidative cyclisation mechanism depicted, hydrometallation or silylation mechanisms may be operative in some instances. It is also likely that the different variants of aldehyde/alkyne couplings proceed by different mechanisms.



Scheme 1.41 Possible Mechanism for the Nickel-Catalysed Cyclisation of Ynals

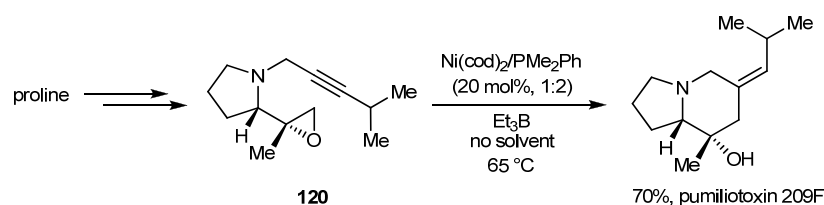
1.4.7 Coupling of Alkynes with Epoxides

Thus far, all the systems considered involve the union of two π -electron systems. Molinaro and Jamison have reported the first examples that deviate from this requirement, with coupling of an alkyne and an epoxide.³³ Both inter- and intramolecular reductive couplings were reported, using triethylborane as a reducing agent, to yield synthetically useful chiral homoallylic alcohols. Internal alkynes were tolerated with most examples involving aryl alkynes or enynes. With respect to the intramolecular reactions, heteroatoms were tolerated in the tether between the alkyne and epoxide, giving rise to a variety of 5- and 6-membered carbo- and heterocyclic rings (Scheme 1.42). All examples involved monosubstituted epoxides, with addition always occurring at the unsubstituted epoxide position.



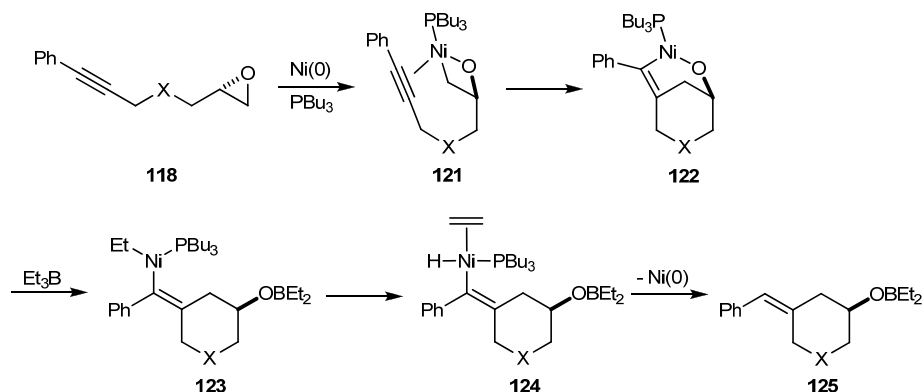
Scheme 1.42 Examples of Alkyne-Epoxy Cyclisation

Woodin and Jamison have used the nickel-catalysed epoxide/alkyne reductive cyclisation as the final step in the total synthesis of both pumiliotoxins 209F and 251D.³⁴ Epoxy alkyne **120**, which was assembled from proline, was cyclised under modified conditions to yield pumiliotoxin 209F in 70% yield (Scheme 1.43). This cyclisation was particularly noteworthy because it was the first example of a successful nickel-catalysed cyclisation between a 1,1-disubstituted epoxide and an alkyne. Through modification of the synthesis of the epoxy alkyne precursor it was also possible to synthesise pumiliotoxin 251F.



Scheme 1.43 Total Synthesis of Pumiliotoxin 209F through Nickel-Catalysed Alkyne-Epoxy Cyclisation

The mechanism proposed by Jamison involves oxidative addition to the epoxide to afford the 4-membered oxametallacycle **121** (Scheme 1.44).³³ Alkyne insertion, followed by reduction of the C-Ni bond by ethyl transfer from boron to nickel, and subsequent β -hydride elimination/reductive elimination would afford the observed products.

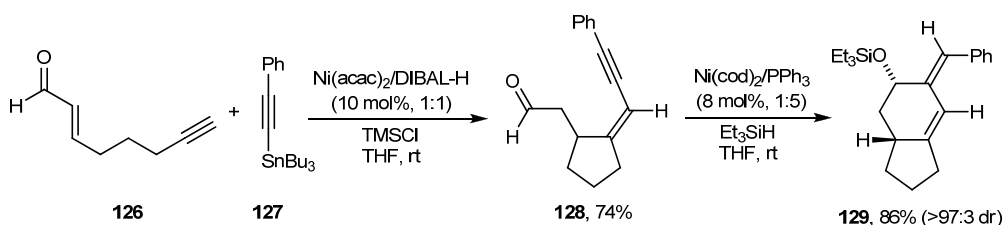


Scheme 1.44 Possible Mechanism for Alkyne-Epoxyde Cyclisation

1.5 Combinations and Domino Reactions

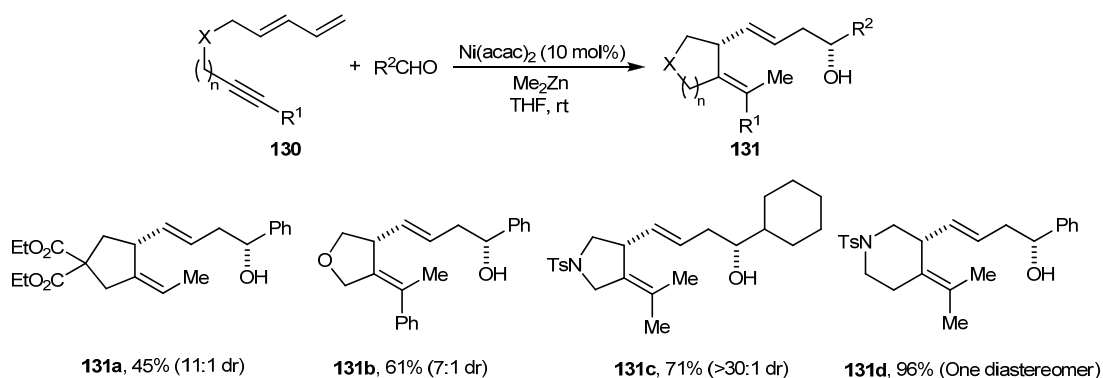
So far we have focused on three-component couplings involving two π -systems and a main-group organometallic reagent or metal hydride. However, several processes have been developed which involve four or more components.

Lozanov and Montgomery have developed a two-step, multicomponent coupling of enals, alkynes and alkynyl tin reagents as a means to synthesise highly functionalised cyclohexanol derivatives (Scheme 1.45).³⁵ Using conditions developed by Ikeda¹¹ enal **126** was cyclised to afford conjugated enyne **128**, containing a tethered aldehyde. Cyclisation of **128** in the presence of $\text{Ni}(\text{cod})_2/\text{PPh}_3$, and using triethylsilane as a stoichiometric reductant, cleanly afforded bicyclononenol **129** in excellent yield and diastereoselectivity.



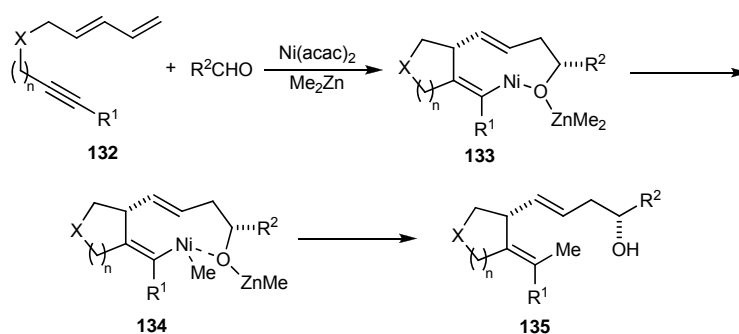
Scheme 1.45 Example of a Two-Step, Multicomponent Coupling

Tamaru and co-workers have reported a highly chemoselective one-pot combination sequence involving a 1,3-diene, an alkyne, an organozinc reagent, and an aldehyde (Scheme 1.46).³⁶ The scope of this four-component coupling was demonstrated to be broad, thereby allowing the rapid assembly of a variety of complex carbo- and heterocyclic structures.



Scheme 1.46 Examples of Nickel-Catalysed Coupling of 1, ω -Dienynes, Aldehydes, and Dimethylzinc

Tamaru proposed a mechanism for these complex coupling reactions which involves oxidative cyclisation of $Ni(0)$ with the aldehyde, alkyne and diene to afford metallacycle **133** (Scheme 1.47). Subsequent migration of a methyl group from dimethylzinc to $Ni(II)$ to generate methylvinylnickel(II) intermediate **134**, followed by reductive elimination generates the desired products.



Scheme 1.47 Possible Mechanism for the Nickel-Catalysed Four-Component Coupling Reaction

1.6 Conclusions

The nickel-catalysed reductive cyclisation of two π -components in the presence of a stoichiometric reductant has emerged as a synthetically useful method to form new carbon-carbon bonds. Using this form of cyclisation, a diverse range of carbo- and heterocyclic ring systems can be constructed, incorporating a wide variety of different functional groups. The scope of this reaction is not just limited to simple three-component couplings, with multicomponent and domino reactions allowing the rapid buildup of molecular complexity from relatively simple starting materials. The broad scope of this reaction has driven much interest in understanding the mechanistic aspects which dictate the synthetic outcome. As we have seen there is no general mechanism that encompasses all reductive cyclisations, but many of those proposed share common features. Driven by recent progress, many research groups are pushing the boundaries in this field in terms of both scope and mechanistic insight.

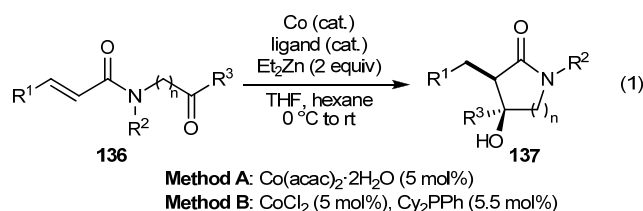
2. Nickel-Catalysed Reductive Aldol Cyclisations: Scope and Mechanistic Insight^{‡37}

2.1 Introduction

In recent years the reductive aldol reaction has emerged as a synthetically useful alternative to the traditional aldol reaction as a means of preparing β -hydroxy carbonyl compounds. Through the reaction of an aldehyde or ketone with an enolate generated *in situ* by the conjugate reduction of an α,β -unsaturated carbonyl compound this reaction has become a powerful method to synthesise new carbon-carbon bonds. Using various metal precatalysts and stoichiometric reductants, a wide variety of inter- and intramolecular reductive aldol reactions have been described.³⁸

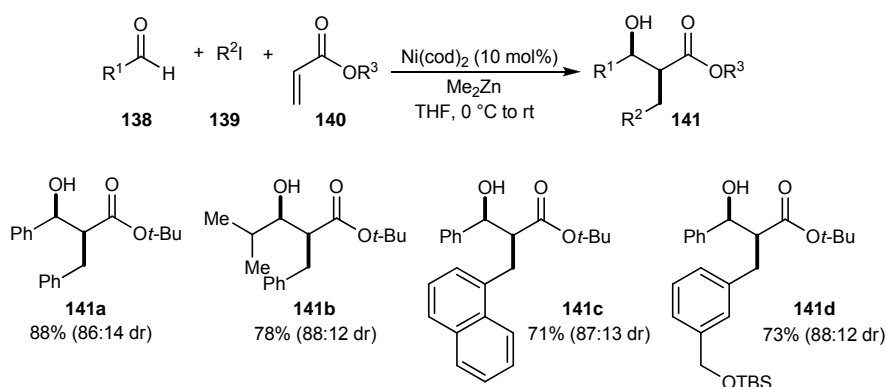
Within the Lam group we have largely focused on using the reductive aldol reaction as a means to synthesise both β -hydroxylactams and β -hydroxylactones. Initially we focused on the use of copper precatalysts in combination with stoichiometric silane reductants as a means to cyclise substrates containing an α,β -unsaturated carbonyl moiety tethered to a ketone through an ester or an amide.³⁹ However, we have recently demonstrated that cobalt salts also function as efficient precatalysts, in the diethylzinc-mediated reductive aldol cyclisation.⁴⁰ This methodology yielded both five and six-membered β -hydroxylactams in 47 to >99% yield, and with generally high levels of diastereoselection (8:1 to >19:1), from amide-tethered precursors (eq 1).

[‡] The results presented in this chapter were obtained in collaboration with Dr Pekka Joensuu and Dr Gordon Murray and therefore results not obtained by myself will be appropriately highlighted.



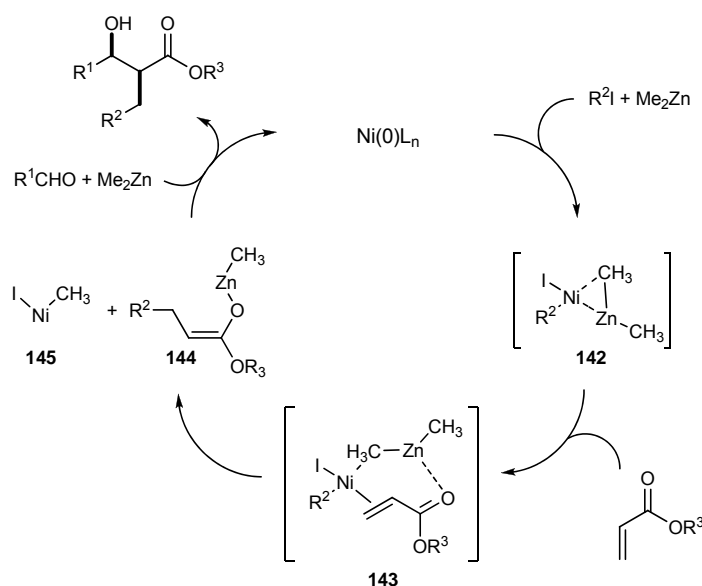
Unfortunately, this methodology was less successful with more highly substituted α,β -unsaturated amides and oxygen-linked precursors, which generally resulted in negligible conversions (<5%). These limitations prompted the group to initiate a programme targeted at the development of new reductive aldol cyclisations and couplings catalysed by nickel.

The emergence of nickel salts as potential precatalysts in reductive and alkylative aldol reactions has only recently been realised. In 2003, Subburaj and Montgomery reported the first example of a nickel-catalysed alkylative aldol reaction.⁴¹ Optimised conditions for this four component coupling involve the use of Ni(cod)₂ as the nickel source and dimethylzinc as the stoichiometric reductant. The reaction showed broad scope with respect to both the aldehyde and aryl iodide (Scheme 2.1). Overall, the yields and diastereoselectivity were good, with the exception of suppressed diastereoselectivity observed in the case of sterically hindered aldehydes.



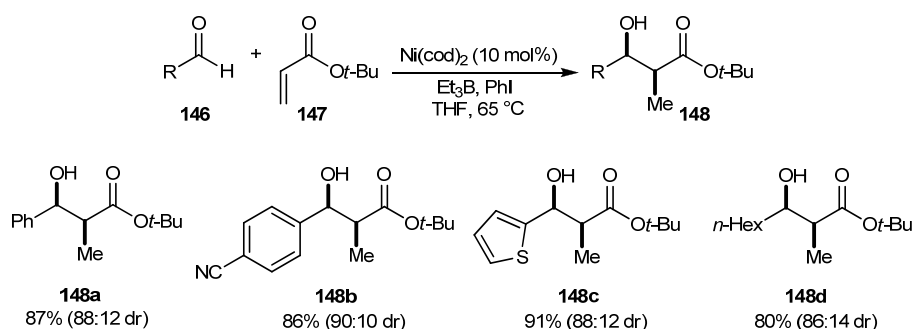
Scheme 2.1 Examples of a Nickel-Catalysed Alkylative Aldol Reaction

Montgomery proposed a mechanism for this transformation, which initially involves oxidative addition of the aryl iodide to Ni(0) to give **142** (Scheme 2.2). Interaction of **142** with the organozinc and α,β -unsaturated ester yields intermediate **143**. The exact mechanism by which **143** is converted to the zinc enolate **144** is unknown but it was speculated that this may involve migratory insertion or oxidative addition, either with or without the involvement of electron transfer/capture pathways. Aldol addition of the zinc enolate to the aldehyde generates the desired product, with concomitant reduction of the Ni(II) species **145** completing the catalytic cycle.



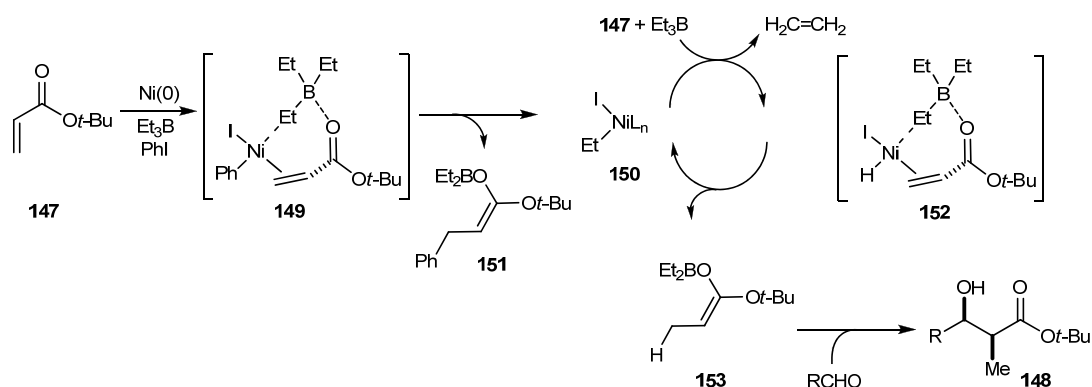
Scheme 2.2 Possible Mechanism for the Nickel-Catalysed Alkylative Aldol Reaction

In 2007 Chrovian and Montgomery reported the first example of a nickel-catalysed reductive aldol reaction by replacing the dimethylzinc, necessary in the alkylative aldol reaction, with triethylborane.⁴² This reaction is high yielding, *syn* selective and tolerant of a wide variety of aromatic and aliphatic aldehydes (Scheme 2.3).



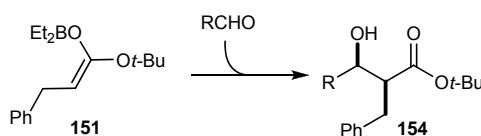
Scheme 2.3 Examples of the Nickel-Catalysed Reductive Aldol Reaction

It was observed during the course of these studies that an aryl iodide was necessary for the reaction to proceed and that a small amount (ca. 5%) of alkylative aldol product was formed in addition to the major product. This product was formed rapidly at the start of the reaction but after this initial burst, its concentration remained constant whilst that of the major product increased. It was therefore suggested that the aryl iodide plays a key role in the initial steps of this transformation. The mechanism proposed by Montgomery involves oxidative addition of Ni(0) to the aryl iodide, and subsequent coordination to acrylate **147** and triethylborane (Scheme 2.4). Migratory insertion and transmetallation affords ethyl(iodo)nickel species **150**. Complexation of ethyl(iodo)nickel species **150** with acrylate **147** and triethylborane, followed by loss of ethylene, generates nickel hydride **152**. Reorganisation of **152** to the boron enolate **153** is accompanied by regeneration of the ethyl(iodo)nickel species **150**, and subsequent *syn*-aldol addition of **153** with the aldehyde affords the desired product.



Scheme 2.4 Possible Mechanism for the Nickel-Catalysed Reductive Aldol Reaction

The formation of small amounts of alkylative aldol by-product was attributed to *syn*-aldol addition of boron enolate **151** to the aldehyde (Scheme 2.5).



Scheme 2.5 Formation of the Alkylative Product

Given the relatively few examples of nickel-catalysed alkylative or reductive aldol reactions, we believed there was scope for development within this field. Thus, in this chapter we report a novel nickel-catalysed reductive aldol protocol developed within our group that can be used to cyclise a diverse range of substrates, which contain α,β -unsaturated carbonyl tethered through an ester or an amide to a ketone. In doing so we will demonstrate that this methodology can be used to overcome many of the problems encountered with our cobalt-based methodology, and thereby promote the cyclisation of less reactive substrates.

2.2 Results and Discussion

2.2.1 Reaction Optimisation and Scope

Our investigation into nickel-catalysed reductive aldol cyclisations commenced with a screening of various nickel salts, ligands and reductants.⁴³ After some optimisation Ni(acac)₂ was identified as a potential precatalyst with diethylzinc as a stoichiometric reductant. Initially these optimised conditions were applied to the cyclisation of various α,β -unsaturated amides tethered to ketones to furnish 4-hydroxypiperidin-2-ones **156a-156m** (Table 2.1). It was demonstrated that a variety of substituents were tolerated at the β -position of the α,β -unsaturated amide component including linear and branched alkyl (entries 1-3, 8-10, and 12), aromatic (entries 4, 7, and 13), and heteroaromatic (entries 5, 6 and 11) groups. In all cases the desired cyclisation

product was obtained in good to excellent yield and with generally high diastereoselectivities ($\geq 9:1$ by ^1H NMR analysis of the unpurified reaction mixtures). The reaction was also tolerant to variation of the ketone component with alkyl (entries 1-7), cycloalkyl (entries 12 and 13) and phenyl (entries 8-11) ketones all participating successfully. Variation of the nitrogen protecting group was also possible with benzyl (entries 1-5 and 9-11), *para*- and *ortho*-methoxyphenyl groups (entries 6-8 and 12 and 13) tolerated. The presence of a pre-existing stereocentre in substrates **155l** and **155m** led to high levels of internal asymmetric induction to provide bicyclic δ -lactams **156l** and **156m** respectively.

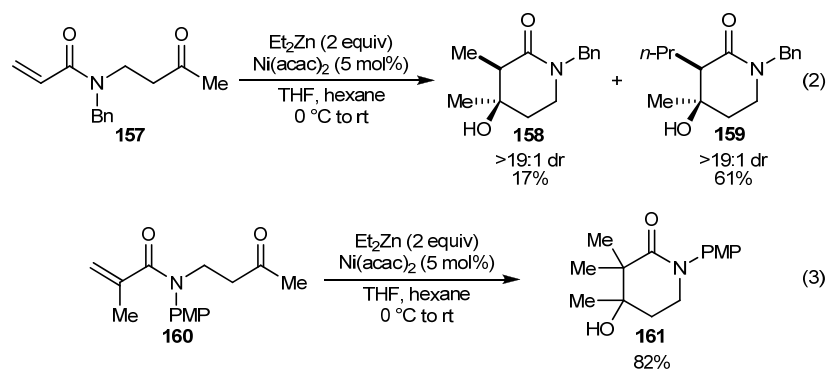
Table 2.1 Nickel-catalysed reductive aldol cyclisation furnishing 4-hydroxypiperidin-ones.^a

$$\text{155a-155m} \xrightarrow[\text{THF, hexane, 0 °C to rt}]{\text{Et}_2\text{Zn (2 equiv), Ni(acac)}_2 \text{ (5 mol\%)}} \text{156a-156m}$$

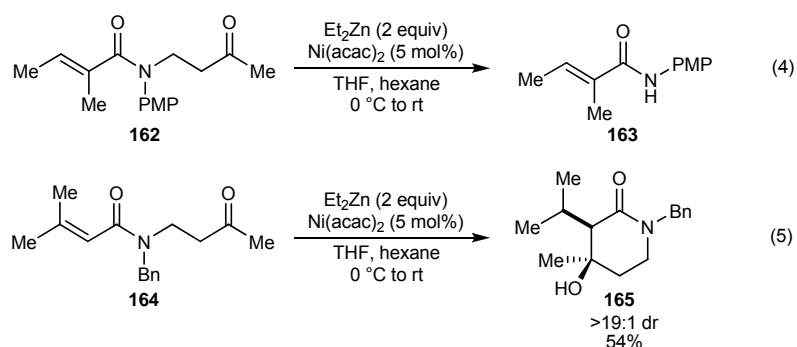
entry	substrate	product	dr ^b	yield (%) ^c
1	R = Me 155a	156a	>19:1	97 ^e
2	R = <i>i</i> -Pr 155b	156b	>19:1	98 ^e
3			>19:1	95 ^e
4	R = Ph 155d	156d	>19:1	97 ^e
5	R = 2-furyl 155e	156e	>19:1	>99 ^e
6			>19:1	75 ^f
7			9:1	82 ^f
8			>19:1	62 ^f
9	R = Me 155i	156i	9:1	84 ^e
10	R = <i>i</i> -Bu 155j	156j	12:1	84 ^e
11	R = 2-furyl 155k	156k	>19:1	79 ^e
12			>19:1 ^d	62
13			>19:1 ^d	50

^a Reactions were conducted using 0.20 mmol of substrate in THF (1.5 mL) and hexane (0.4 mL). ^b Determined by ¹H NMR analysis of the unpurified reaction mixtures. ^c Isolated yield of major diastereomer. ^d Here dr = (major isomer):(Σ other isomers). PMP = *para*-methoxyphenyl. OMP = *ortho*-methoxyphenyl. ^e Results obtained by Dr Pekka Joensuu. ^f Results obtained by Dr Gordon Murray.

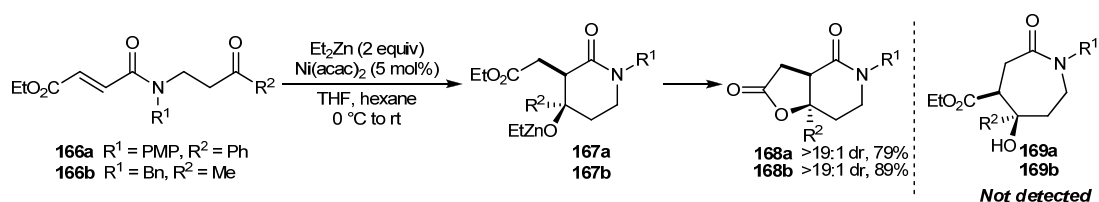
Problems were encountered in attempting to cyclise simple β -unsubstituted acrylamide derivatives, with *alkylative* aldol cyclisation⁴⁴ competing with the desired reductive cyclisation as the dominant reaction pathway. For example acrylamide **157** provided desired product **158** in only 17% yield, with the major product obtained being **159**, derived from ethyl conjugate addition and aldol cyclisation (eq 2; result obtained by Dr Gordon Murray). However, substitution at the α -position of the acrylamide re-established reductive cyclisation as the dominant pathway. This is illustrated in the reductive cyclisation of methylacrylamide **160** to provide lactam **161**, containing two contiguous quaternary centres, in 82% yield (eq 3; result obtained by Dr Gordon Murray).



Unfortunately, our efforts to extend the scope of these reactions to more highly substituted α,β -unsubstituted amides were only partially successful. Tiglic acid derived amide **162** did not undergo cyclisation, with the elimination product isolated instead (eq 4; result obtained by Dr Gordon Murray). However the β,β -disubstituted α,β -unsubstituted amide, **164**, was successfully cyclised to obtain the desired lactam, **165**, in 54% yield (eq 5; result obtained by Dr Gordon Murray).

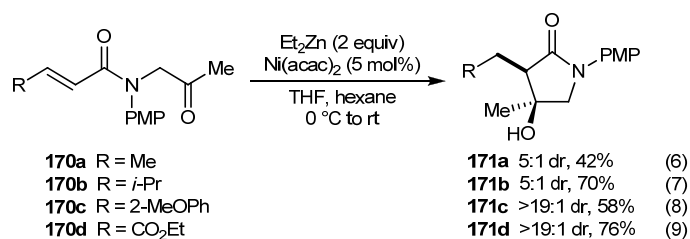


The cyclisation of β -ester-substituted α,β -unsaturated amides **166a** and **166b** proved interesting from a chemoselectivity viewpoint, as these substrates have the potential to cyclise either α -to the amide or α -to the ester. In the event, bicyclic products **168a** and **168b**, resulting from cyclisation α -to the amide, were isolated in excellent yield with none of the alternative regioisomeric products, **169a** and **169b**, observed in the product mixtures (Scheme 2.6; results obtained by Dr Pekka Joensuu).



Scheme 2.6 Chemoselective Cyclisation of β -Ester-Substituted α,β -Unsaturated Amides **166a** and **166b**

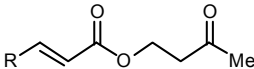
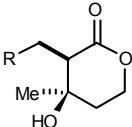
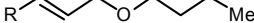
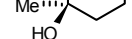
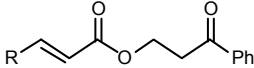
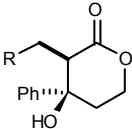
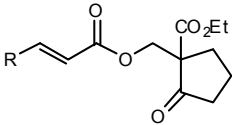
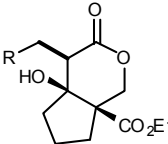
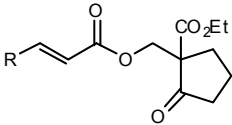
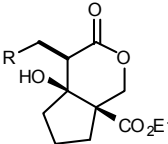
This methodology was also applicable to the synthesis of five-membered lactams (eqs 6-9; results obtained by Dr Gordon Murray). Again, variation of the substituent in the β -position of the α,β -unsaturated carbonyl component was demonstrated with alkyl, (eqs 6 and 7), aromatic (eq 8) and ester groups (eq 9) all tolerated.



In order to broaden the scope of this methodology, we next examined the cyclisation of the corresponding α,β -unsaturated esters. Cyclisation of such substrates using Co(acac)₂·2H₂O as a precatalyst had previously proved unsuccessful, with only negligible conversions (<5%) observed. However using the Ni(acac)₂/Et₂Zn combination we were pleased to observe that a wide variety of α,β -unsaturated esters were successfully cyclised to afford the desired β -hydroxylactones **173a-173j** in good to excellent yields and with high diastereoselectivities (Table 2.2). It was demonstrated that these reactions were tolerant of substitution at both the α,β -unsaturated carbonyl component and ketone. Again, pre-existing stereocentres in substrates **172h-172j** led to high levels of internal asymmetric induction (entries 8-10). With substrates **172f** and **172g** it was also noted that small quantities of the corresponding alkylative aldol cyclisation products were observed (entries 6 and 7).

Table 2.2. Nickel-catalysed reductive aldol cyclisation furnishing β -hydroxylactones.^a

$\text{R}^1\text{-CH=CH-C(=O)O-CH}_2\text{-CH}_2\text{-C(=O)R}^2$ (**172a-172j**) $\xrightarrow[\text{THF, hexane, 0 } ^\circ\text{C to rt}]{\text{Et}_2\text{Zn (2 equiv), Ni(acac)}_2 \text{ (5 mol\%)}}$ $\text{R}^1\text{-CH}_2\text{-CH(OH)-CH}_2\text{-CH}_2\text{-C(=O)O-CH}_2\text{-R}^2$ (**173a-173j**)

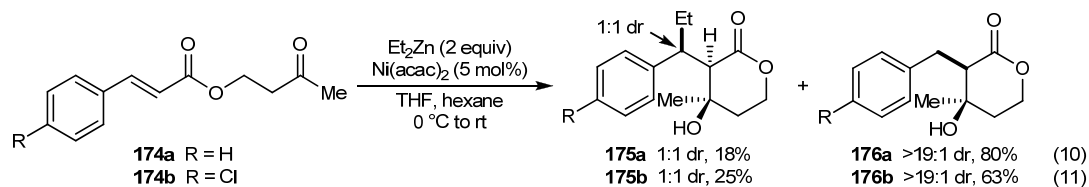
entry	substrate	product	dr ^b	yield (%) ^c	
1	R = <i>i</i> -Bu 172a	173a	>19:1	77 ^d	
2	 R = CH ₂ CH ₂ Ph 172b		173b	>19:1	85 ^d
3	 R = 4-MeOPh 172c		173c	>19:1	76 ^d
4	R = 2-furyl 172d	173d	>19:1	81 ^d	
5	R = <i>i</i> -Bu 172e	173e	5.5:1	84 ^{d,e}	
6	 R = CH ₂ CH ₂ Ph 172f		173f	≥10:1	76 ^{d,f}
7	R = 2-furyl 172g	173g	n.d. ^f	75 ^{d,g}	
8	R = Me 172h	173h	>19:1 ^h	88	
9	 R = <i>i</i> -Pr 172i		173i	>19:1 ^h	74
10	 R = Ph 172j		173j	>19:1 ^h	73

^a Reactions were conducted using 0.20 mmol of substrate in THF (1.5 mL) and hexane (0.4 mL).

^b Determined by ¹H NMR analysis of the unpurified reaction mixtures. ^c Isolated yield of major diastereomer. ^d Results obtained by Dr Pekka Joensuu. ^e Isolated as an inseparable 5.5:1 mixture of diastereomers. ^f Accompanied by <5% of alkylative cyclisation product as an inseparable impurity. Cited yield of **173f** has been adjusted to reflect this impurity. ^g Accompanied by *ca.* 10% of alkylative cyclisation product as an inseparable impurity, making determination of the diastereomeric ratio of **173g** difficult. Cited yield of **173g** has been adjusted to reflect this impurity. ^h Here dr = (major isomer):(Σ other isomers).

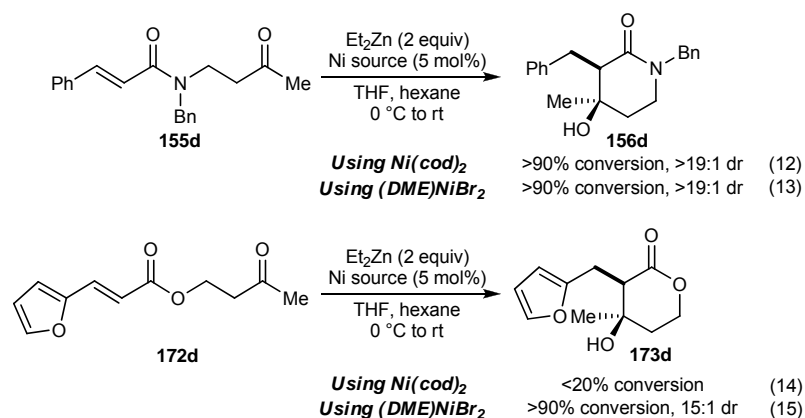
During these studies an interesting electronic effect was observed with cinnamic derivatives **172c** and **174a** and **174b**. Although *p*-methoxy-substituted precursor **172c** gave the desired reductive aldol product **173c** in 76% yield (Table 2.2, entry 3), less electron-rich substrates **174a** and **174b** provided significant quantities of alkylative aldol products **175a** and **175b** (eqs 10 and 11; results obtained by Dr

Pekka Joensuu). These results appear to suggest that as the aromatic group becomes more electron-deficient the degree of alkylative aldol cyclisation becomes more significant.



2.2.2 Mechanistic Considerations

Numerous mechanisms have been proposed to explain the outcome of nickel-catalysed reductive couplings and cyclisations (Chapter 1). However, it is generally accepted that the active oxidation state of nickel in these transformations is Ni(0). In cases where Ni(II) salts are used as precatalysts, these are reduced *in situ* to Ni(0) through the use of reductants such as diethylzinc. Although we assume that this is the case in these reactions, we cannot exclude the possibility that the active catalyst is actually a Ni(II) species. Therefore, in order to gain an insight as to the oxidation state of our active species, we repeated two representative reactions using $\text{Ni}(\text{cod})_2$ in place of $\text{Ni}(\text{acac})_2$ with the premise that if Ni(0) was the true active species cyclisation would occur. In the event, cyclisation was observed in both cases (eqs 12 and 14); however the efficiencies of these reactions were markedly different. Reaction of cinnamic amide derivative **155d** with $\text{Ni}(\text{cod})_2$ afforded the desired lactam, **156d**, with both high conversion and diastereoselectivity (>90%, >19:1). These results compare favourably with those obtained with $\text{Ni}(\text{acac})_2$ (eq 12, compare with Table 2.1, entry 4). However $\text{Ni}(\text{cod})_2$ functioned poorly compared to $\text{Ni}(\text{acac})_2$ with ester-tethered substrate **172d**, with lactone **173d** being obtained in <20% conversion (eq 14, compare with Table 2.2, entry 4).

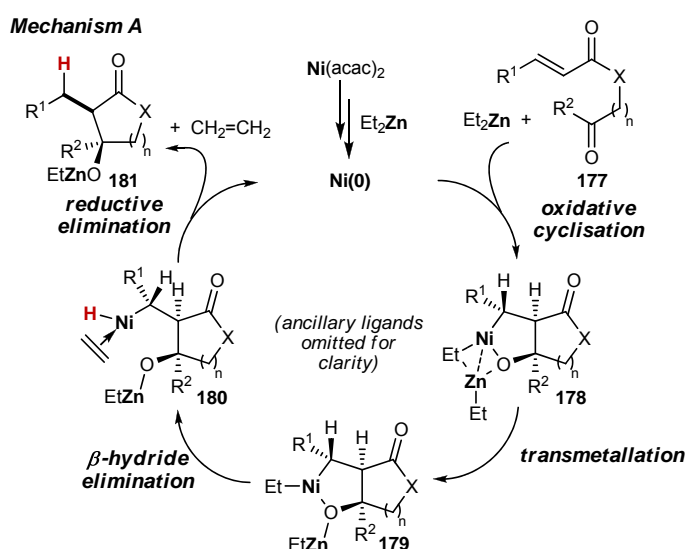


Although there are examples of reactions involving main group organometallic reagents where the catalytic efficiencies of $\text{Ni}(\text{cod})_2$ and $\text{Ni}(\text{acac})_2$ have proven to be essentially indistinguishable,⁴⁵ this is not always the case. In fact there is an increasing awareness that olefins, present as ligands or as exogenous additives, do not always act as innocent bystanders in transition-metal catalysed reactions.⁴⁶ It is therefore possible that the cyclooctadiene ligands present in $\text{Ni}(\text{cod})_2$ are in some way inhibiting the reaction of ester-tethered substrates and therefore reducing the reaction efficiency.

The cyclisations of substrates **155d** and **172d** were repeated using $(\text{DME})\text{NiBr}_2$ as a precatalyst with both cyclisations proceeding with high conversion and diastereoselectivity (eqs 13 and 15). These results further support the hypothesis that the inferiority of $\text{Ni}(\text{cod})_2$ compared with $\text{Ni}(\text{acac})_2$ for ester-tethered substrates is due to an adverse effect of the cyclooctadiene ligands in $\text{Ni}(\text{cod})_2$ rather than some beneficial role played by the acetylacetonate ligands or Zn -acac byproducts resulting from the use of $\text{Ni}(\text{acac})_2$.

Having established that the likely active oxidation state of our catalyst in these reactions is $\text{Ni}(0)$, our focus turned to the mechanism by which these transformations occur. One possible catalytic cycle is depicted in Scheme 2.7 (Mechanism A). This mechanism is initiated by oxidative cyclisation of $\text{Ni}(0)$ with the alkene and ketone

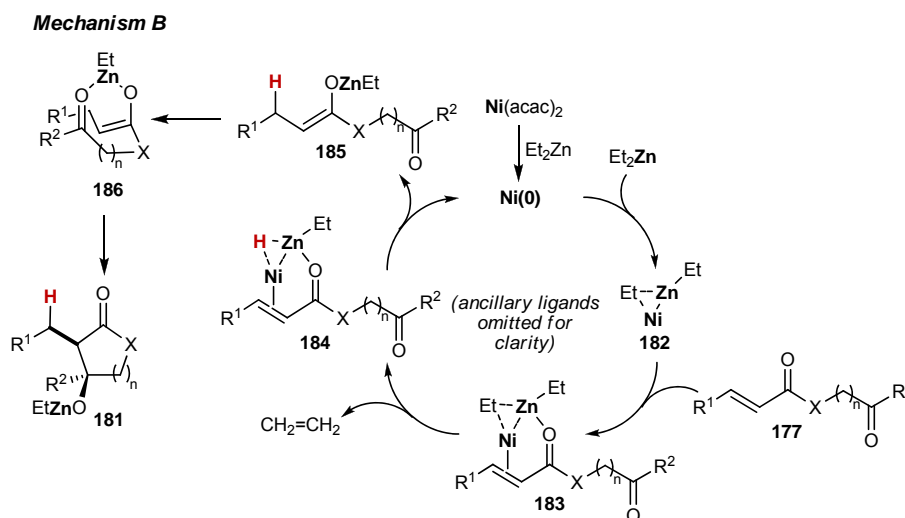
of substrate **177** to yield oxanickellacycle **178**. In this step of the catalytic cycle we suggest that the diethylzinc has a dual role by (i) Lewis acid activation of the ketone through binding with zinc, and (ii) Lewis basic activation of Ni(0) through a three-center two-electron bridging interaction of a zinc-ethyl bond.⁴⁷ Cleavage of oxanickellacycle **178** by transmetalation affords nickel-ethyl species **179**, which then undergoes β -hydride elimination to generate nickel hydride **180**. Finally, reductive elimination of **180** provides zinc alkoxide (which would be protonated upon workup to give the product), ethylene and Ni(0), hence completing the catalytic cycle. The relative stereochemistries of the major diastereomers obtained in these reactions can therefore be explained by the preferential formation of the bicyclic metallacycle **178** containing a *cis*-ring junction, as opposed to a likely higher energy *trans*-ring junction.



Scheme 2.7 Possible Reaction Mechanism for the Nickel-Catalysed Reductive Aldol Cyclisation which involves Metallacycle Formation

An alternative catalytic cycle, which involves discrete enolate intermediates, is illustrated in Scheme 2.8 (Mechanism B). In this mechanism interaction of Ni(0) with diethylzinc leads to formation of intermediate **182**, containing a three-center two-electron bridging interaction.⁴⁷ Coordination of **182** to substrate **177** then

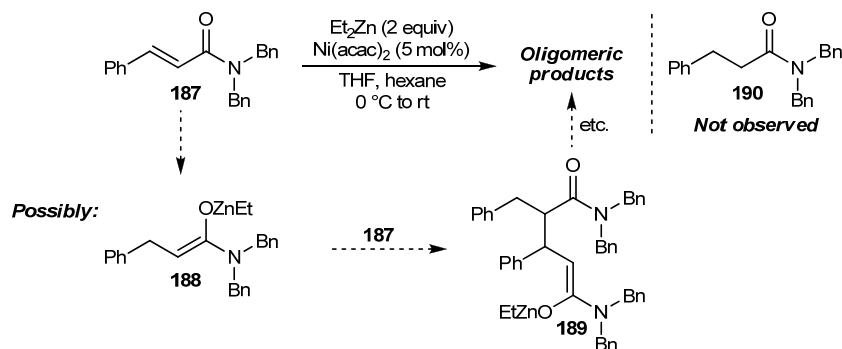
provides **183** which can undergo β -hydride elimination to provide nickel hydride **184**. Reorganisation of **184** then occurs to provide zinc enolate **185**, which undergoes aldol cyclisation to **181**, regenerating Ni(0) to complete the catalytic cycle. Within this mechanistic framework, the observed stereochemical outcome of the reactions may be explained by preferential formation of the (*Z*)-zinc enolate **185**, along with a chelated Zimmerman-Traxler-type transition state **186**.⁴⁸



Scheme 2.8 Alternative Mechanism for the Nickel-Catalysed Reductive Aldol Cyclisation which involves Zinc Enolate Formation

Using these two possible mechanisms we can explain the formation of the alkylative aldol cyclisation products that we observed in varying quantities from precursors **157** (eq 2), **172f** and **172g** (Table 2.2, entries 6 and 7), and **174a** and **174b** (eqs 10 and 11). If mechanism B is in operation, specific steric and/or electronic properties of these substrates may enable conjugate addition from **183** to compete with β -hydride elimination to **184**. Alternatively, if reductive elimination from **179**, in mechanism A, competes effectively with β -hydride elimination to **180**, formation of alkylative aldol product would be expected. However, the isolation of alkylative cyclisation products **175a** and **175b** (eqs 10 and 11) as 1:1 mixtures of diastereomers might be more difficult to rationalise by a metallacycle pathway, assuming all steps in mechanism A are stereospecific.

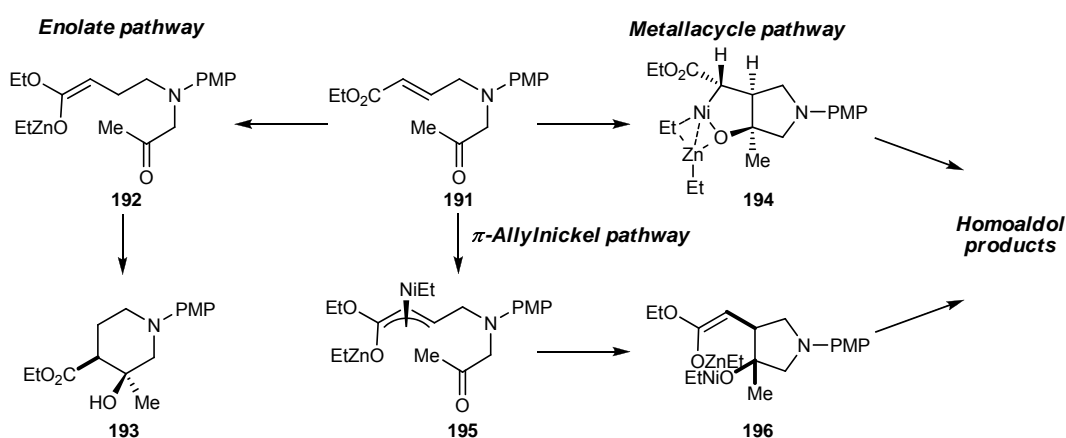
Having proposed these two possible catalytic cycles for the nickel-catalysed reductive aldol cyclisation, our next task was to develop experiments whereby we could provide evidence to support either mechanism. We began with an experiment to establish whether mechanism B (Scheme 2.8) is possible by subjecting α,β -unsaturated amide **187**, lacking the pendant ketone electrophile, to our standard reaction conditions (Scheme 2.9; result obtained by Dr Pekka Joensuu). In principle, mechanism B does not require the participation of the ketone until zinc enolate **185** is formed and therefore we might expect to observe the simple conjugate reduction product **190**. However, in mechanism A (Scheme 2.7) the ketone is an essential component for oxidative cyclisation to occur and therefore if this mechanism is in operation we would expect no reaction to occur. In the event, exposure of **187** to our standard conditions provided only a complex mixture, which appeared to be composed of oligomeric products. Although disappointing, the failure to detect **190** does not rule out mechanism B since the zinc enolate **188**, which would result from conjugate reduction of **187**, could react with additional starting material **187** in a Michael addition to provide a second zinc enolate **189**, which could then lead to further oligomeric products.



Scheme 2.9 Attempted Conjugate Reduction of **187**

The next experiment we envisaged that might shed light on which of these two possible mechanisms is in operation was to analyse the products obtained upon subjecting substrates which differ in terms of connectivity to our standard nickel

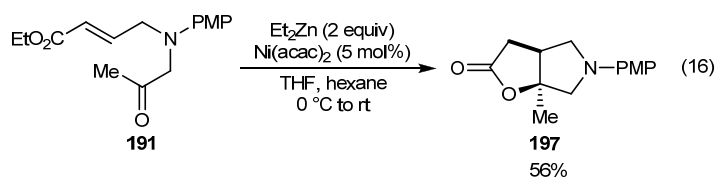
catalysed reductive aldol cyclisation conditions. Thus far, all the substrates we have described have the ketone tethered to the α,β -unsaturated carbonyl *via* an amide or ester linkage and these precursors cyclise to yield the same product whichever of the two possible mechanisms is in operation. This is not the case with substrates such as **191** (Scheme 2.10), which are tethered to the α,β -unsaturated carbonyl through the β -carbon. In this case reductive aldol product **193** would be obtained, if a mechanism analogous to that shown in Scheme 2.8 was operative, as a metallacyclic pathway (analogous to mechanism A, Scheme 2.7) would be precluded on the basis of geometric constraints. However, if products resulting from cyclisation at the β -position were formed, a mechanism (akin to that shown in Scheme 2.7) involving oxanickellacycle **194** could be responsible. A third option that is relevant in this case, but which could not explain the cyclisation of the amide- and ester-tethered substrates, involves Et_2Zn -assisted oxidative addition of $\text{Ni}(0)$ to the α,β -unsaturated ester to form π -allylnickel complex **195**, followed by migratory insertion of the ketone to give **196**.



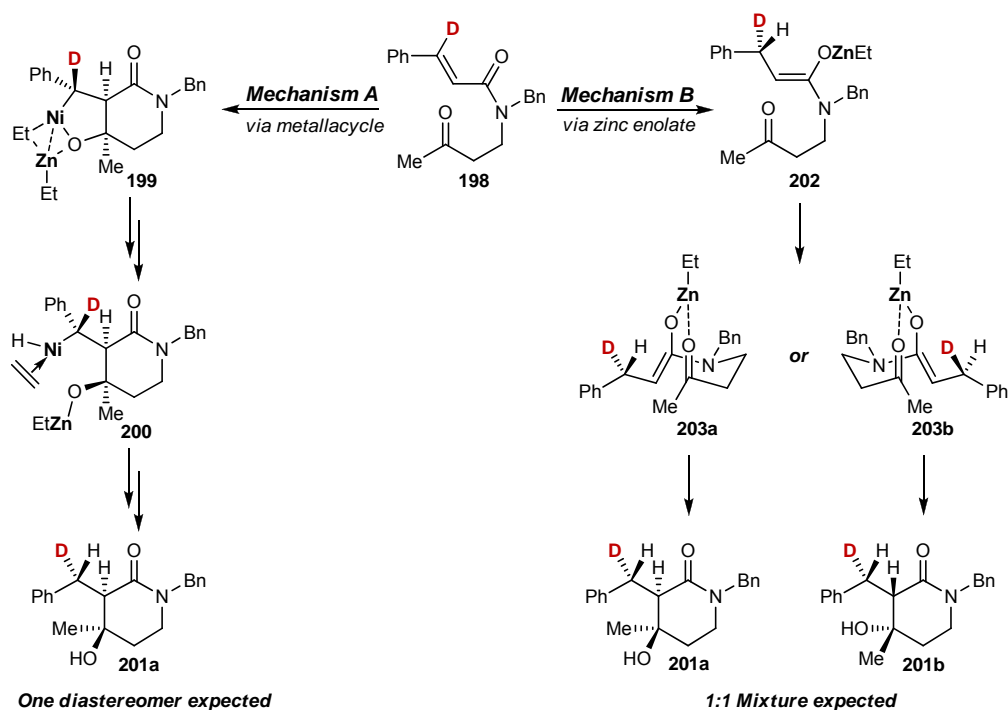
Scheme 2.10 Possible Cyclisation Outcomes for Substrate **191**

On subjecting **191** to our standard reaction conditions, bicyclic lactone **197** was obtained in 56% yield (eq 16), with no evidence of the corresponding reductive aldol product **193**. Therefore, an enolate mechanism can be ruled out for the cyclisation of **191**, leaving metallacycle or π -allylnickel pathways as viable options. Although this

result provides strong evidence as to the probable mechanism for the cyclisation of **191**, it does not provide definitive proof that a metallacyclic pathway operates for the cyclisation of the amide- and ester-tethered precursors, nor does it allow us to confidently exclude an enolate mechanism for these substrates. Nevertheless, the reaction of **191** still represents an important experiment, as the result at least demonstrates the possibility of metallacycle participation in the cyclisation of α,β -unsaturated carbonyl and ketone functional groups using $\text{Ni}(\text{acac})_2/\text{Et}_2\text{Zn}$.

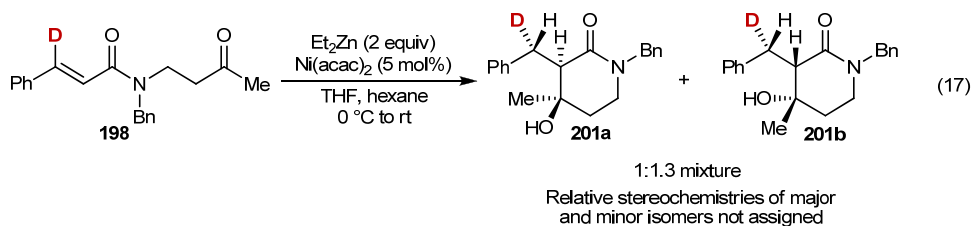


Our next attempt to discriminate between mechanism A and B involved the analysis of the stereochemical outcome of the cyclisation of deuterium-labelled substrate **198**. If the reaction proceeds *via* the metallacycle-based mechanism (Mechanism A, Scheme 2.7) the concerted nature of the oxidative cyclisation would be expected to provide metallacycle **199** with the relative stereochemistry shown (Scheme 2.11). With the subsequent reductive elimination of nickel hydride **200** proceeding with retention of configuration, only one diastereomer, **201a**, of the cyclised product would be expected. Alternatively, if mechanism B is in operation we would expect a 1:1 mixture of the two product diastereomers **201a** and **201b**, as the diastereomeric Zimmerman-Traxler-type transition states **203a** and **203b** differ only with respect to the deuterium label and so would be expected to possess virtually identical energies.

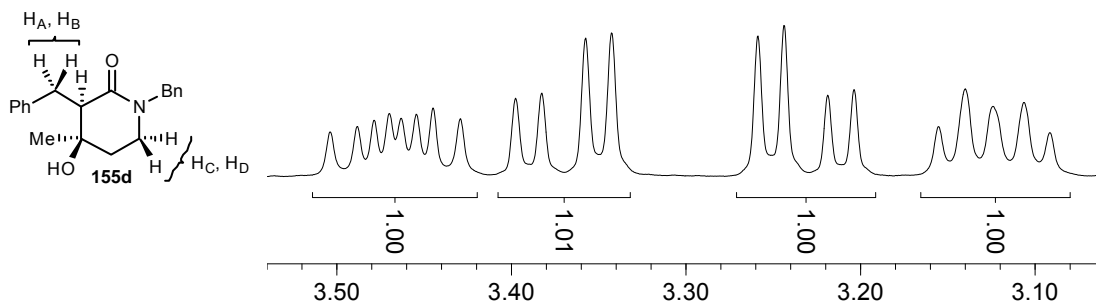


Scheme 2.11 Expected Stereochemical Outcomes of Reductive Cyclisation of Deuterium-Labelled Substrate **198** under Mechanisms A and B

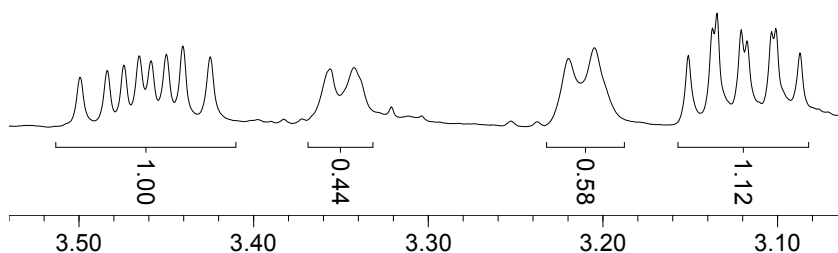
In the event, exposure of **198** to our standard nickel-catalysed reductive cyclisation conditions afforded a 1:1.3 mixture of inseparable diastereomeric products **201a** and **201b** (relative stereochemistries of the major and minor diastereomers are not assigned) as determined by ^1H NMR analysis of the unpurified reaction mixture (Scheme 2.12, spectrum b and equation 17; result obtained by Dr Pekka Joensuu). The nonequimolar ratio of diastereomers obtained was confirmed after removal of trace impurities by column chromatography,⁴⁹ and this result proved to be repeatable.



(a) Unlabelled reference



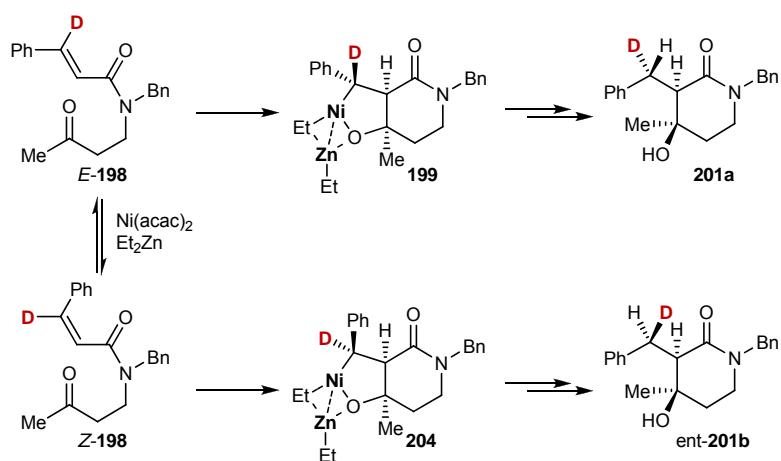
(b) Unpurified product **201a/201b** obtained using Ni(acac)₂/Et₂Zn



Scheme 2.12 Reductive Cyclisation of Deuterium-Labelled Substrate **198** and ¹H NMR Spectra of Unlabelled Reference and Diastereomeric Products Obtained

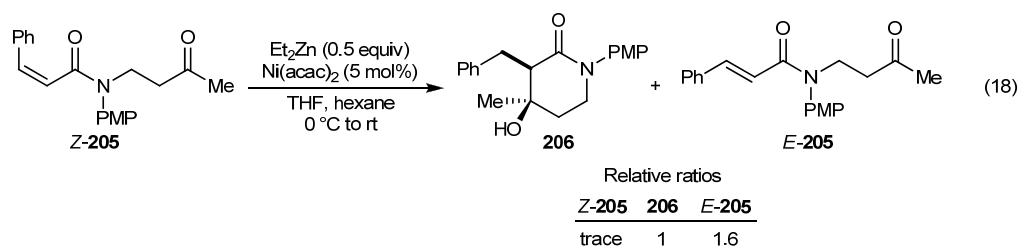
This result appears to provide strong evidence against mechanism A. However, one factor which we have not taken into account, and which may complicate the analysis of this deuterium-labeling study, is the possibility that the alkene of the α,β -unsaturated carbonyl moiety undergoes *E/Z* equilibration during these reactions (Scheme 2.13). Although (*Z*)-**198** is likely to be present as only a minor component in an *E/Z* equilibrium mixture, this isomer could be important in determining the stereochemical outcome of the reaction if Curtin-Hammett-type kinetics apply.⁵⁰ The implication of Curtin-Hammett-kinetics in this context means that if *E/Z* conversion

is rapid, and each isomer irreversibly forms a different product, the ratio of the two product diastereomers will depend on the reactivity of the two isomer and not the equilibrium constant between them. Hence, if (*Z*)-**198** displays a comparable or higher reactivity compared to that of (*E*)-**198** we might expect formation of both diastereomers **201a** and **201b** and therefore mechanism A cannot be discounted.

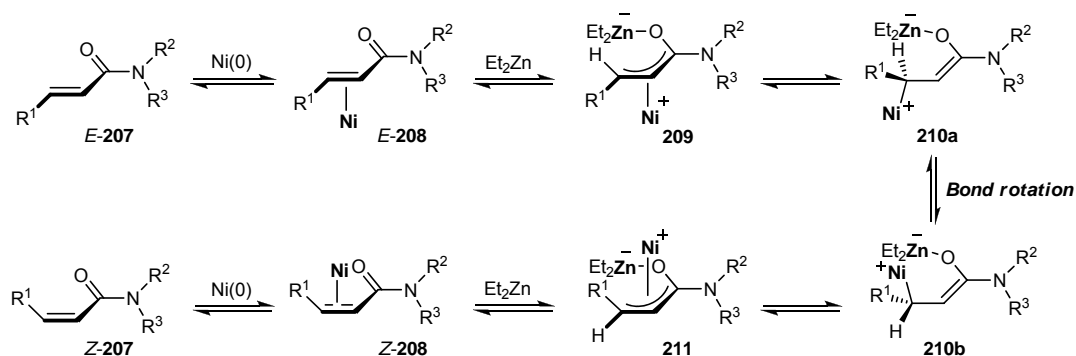


Scheme 2.13 *E*- to *Z*-Alkene Isomerisation Could Allow a Mixture of **201a** and **201b** to be obtained via a Metallacycle Mechanism

To determine whether attainment of *E/Z* equilibrium is possible, we prepared (*Z*)-cinnamic amide (*Z*)-**205** and allowed the cyclisation of this compound to proceed to partial completion by using only 0.5 equivalents of Et_2Zn , as opposed to the 2 equivalents used under our standard conditions (eq 18). Examination of the ^1H NMR spectrum of the unpurified reaction mixture revealed the presence of lactam **206**, in addition to uncyclised material which had undergone virtually complete isomerisation (*E/Z* >19:1) to the more thermodynamically stable *E*-isomer, (*E*)-**205**. Therefore, mechanism A cannot be excluded on the basis of the results of eq 18.

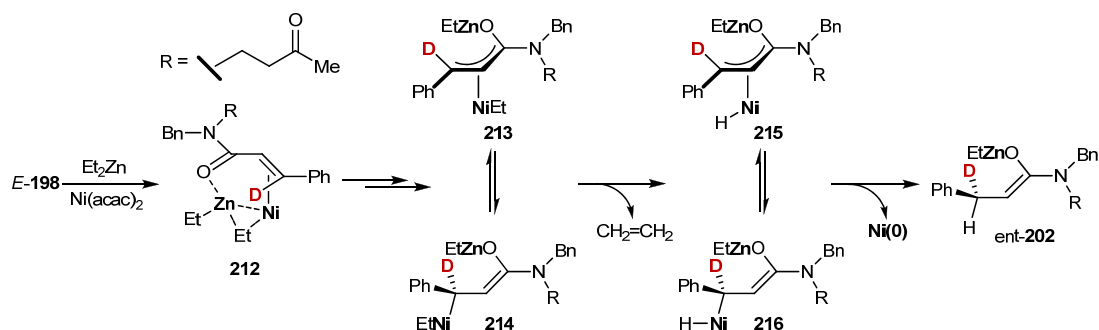


We suggest that alkene isomerisation occurs *via* the formation of a π -allylnickel species. The formation of such species *via* oxidative addition of Ni(0) to α,β -unsaturated aldehydes in the presence of trialkylsilyl chlorides has precedent in the pioneering studies by Mackenzie and co-workers.¹² Therefore, on the basis of this precedent, we propose that *E/Z* equilibration is initiated by coordination of Ni(0) to α,β -unsaturated amide (*E*)-**207** to provide η^2 -coordinated complex (*E*)-**208**, followed by Et₂Zn-assisted oxidative addition to provide π -allylnickel complex **209** (Scheme 2.14). A hapticity change from η^3 to η^1 to give **210a** would then allow bond rotation to occur to provide **210b**. Re-establishment of η^3 hapticity to give π -allylnickel complex **211**, followed by reductive elimination to (*Z*)-**208** and decomplexation, would then furnish the isomerised α,β -unsaturated amide (*Z*)-**207**. The entire process is of course reversible. It should be stated that, for the purposes of simplicity, no three-centre two-electron bridging interaction of the type depicted in structure **183** (Scheme 2.8) and in structure **212** (Scheme 2.15) between nickel, zinc, and an ethyl ligand has been shown for structures **208-211** in Scheme 2.14.



Scheme 2.14 Possible Mechanism for *E/Z* Isomerisation

Having determined that mechanism A cannot be excluded on the basis of these deuterium-labelling studies, our attention turned to whether we could explain the ratio of diastereomeric products **201a** and **201b** in the context of mechanism B. In the simplified representation of mechanism B, we assume that coordination of the pendant ketone in Zimmerman-Traxler-type transition states **203a** and **203b** only occurs after zinc enolate **202** has formed, which should then provide a 1:1 mixture of **201a** and **201b** (Scheme 2.11). However, if we consider the formation of the zinc enolate in more detail (Scheme 2.15) we can see that if the Lewis basic ketone is associated with the nickel and/or zinc centre in any of the intermediates **213-216**, this would place the ketone on one particular diastereotopic face. If this degree of association remains significant until formation of the zinc enolate (ent-**202** in the case of Scheme 2.15), and aldol cyclisation is able to occur before the ketone has the opportunity to fully establish equilibrium in interchanging between the two diastereotopic enolate faces, a nonequimolar distribution of diastereomers would result. Therefore, mechanism B remains a possibility.



Scheme 2.15 Zinc Enolate Formation *via* π -Allylnickel Species

Throughout the course of these mechanistic investigations we have discussed many complex issues and therefore it is important to summarise the key facts. We now have strong evidence that the active oxidation state for the nickel in these reductive aldol cyclisations is Ni(0) and we have demonstrated that *in situ* formation of this active species, from Ni(acac)₂ and Et₂Zn, is in fact superior to the use of Ni(0)

catalysts such as Ni(cod)₂. We have demonstrated that substrate **191** containing a ketone connected to an α,β -unsaturated carbonyl through the β -carbon provides reductive homoaldol product **197**, rather than reductive aldol product **193** and therefore suggests metallacycle or π -allylnickel mechanisms as possible pathways. Finally we have revealed that *E/Z* isomerisation of the α,β -unsaturated carbonyl component can occur under our reaction conditions. Unfortunately, the implication of this phenomenon is that a deuterium-labeling study designed specifically to distinguish between alternative metallacycle and enolate pathways does not allow us to exclude either of these mechanisms.

2.3 Conclusions

In this chapter we have shown that through the use of Ni(acac)₂ as a precatalyst and with the addition of stoichiometric quantities of diethylzinc reductant, we can cyclise a variety of α,β -unsaturated carbonyl compounds tethered to ketones through either an amide or ester to synthesise both β -hydroxylactams and β -hydroxylactones. The reaction is tolerant to variation at both the β -position of the α,β -unsaturated carbonyl component, ketone and where applicable the nitrogen protecting group, yielding the desired products in good to excellent yield and with high levels of diastereoselectivity. In addition to demonstrating the synthetic potential of this reaction, we have attempted to understand the mechanism by which it occurs. To this end we have designed various experiments to try and distinguish which of the two most plausible mechanisms is in operation. But despite all our efforts we have been unable to provide definitive proof to discount either of the two mechanisms and have in fact revealed the complex nature of these reactions. However, we hope that the reactions described herein and the mechanistic information we have provided will stimulate the development of further nickel-catalysed reductive coupling and cyclisation reactions that will be of broad utility.

2.4 Experimental

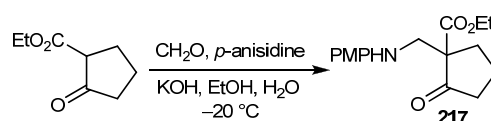
General Information

All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. CH₂Cl₂ and THF were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontour.com 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40-60 °C. All commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilen 60F₂₅₄ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.⁵¹ Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in CHCl₃. ¹H NMR spectra were recorded on a Bruker DMX500 (500 MHz) spectrometer, Bruker DPX360 (360 MHz) spectrometer or a Bruker ARX250 (250 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard (CDCl₃ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ¹³C NMR spectra were recorded on a Bruker DPX360 (90.6 MHz) spectrometer or a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard (CDCl₃ at 77.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer or a Finnigan MAT 95XP spectrometer at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea, or on a

Finnigan MAT 900 XLT spectrometer or a Kratos MS50TC spectrometer at the School of Chemistry, University of Edinburgh. Stated calculated mass values refer to that of the *ion* (i.e. the actual species being detected), *not* that of the neutral parent compound.

Preparation of Aminoketones

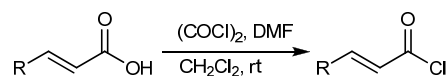
1-[(4-Methoxyphenyl)aminomethyl]-2-oxocyclopentanecarboxylic acid ethyl ester (**217**)



A solution of *p*-anisidine (4.73 g, 38.4 mmol) and aqueous formaldehyde solution (37% wt in H₂O, 2.88 mL, 38.4 mmol) in EtOH (200 mL) was stirred at room temperature for 10 min. Ethyl 2-oxocyclopentanecarboxylate (4.00 g, 25.6 mmol) was added in one portion, the resulting mixture was cooled to –20 °C, and KOH (4.31 g, 76.8 mmol) was then added portionwise over 5 min. The reaction mixture was stirred at –20 °C for 30 min and then poured into saturated aqueous NH₄Cl solution (200 mL). The mixture was extracted with CH₂Cl₂ (3 x 150 mL), and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petrol) gave the *aminoketone* **217** (7.01 g, 94%) as a pale brown oil. IR (film) 3388 (NH), 2959, 1747 (C=O), 1719 (C=O), 1514, 1465, 1234, 1176, 1036, 822 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 6.76 (2H, dm, *J* = 9.0 Hz, ArH), 6.60 (2H, d, *J* = 9.0 Hz, ArH), 4.16 (2H, qd, *J* = 7.1, 1.2 Hz, OCH₂CH₃), 3.73 (3H, s, OCH₃), 3.48 (1H, d, *J* = 13.1 Hz, CH₂N), 3.42 (1H, d, *J* = 13.1 Hz, CH₂N), 2.56–2.41 (2H, m, CH₂CH₂CH₂), 2.34–1.93 (5H, m, CH₂CH₂CH₂ and NH), 1.23 (3H, t, *J* = 7.1 Hz, OCH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 214.7 (C), 170.9 (C), 152.3 (C), 142.2 (C), 114.7 (2 x CH), 114.5 (2 x CH), 61.5 (CH₂), 61.0 (C), 55.6 (CH₃), 47.7 (CH₂), 38.1 (CH₂), 32.0 (CH₂), 19.6 (CH₂), 13.9 (CH₃).

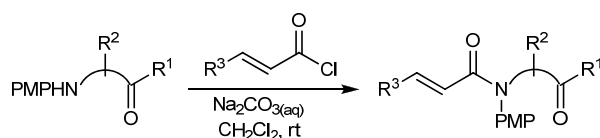
Preparation of α,β -Unsaturated Acid Chlorides: General Procedure

A

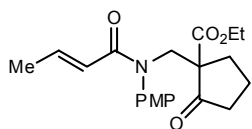


Oxalyl chloride (1.10 equiv) was added dropwise over 2 min to a solution of the appropriate α,β -unsaturated carboxylic acid (1.00 equiv) and DMF (0.25 equiv) in CH_2Cl_2 (0.55 M with respect to carboxylic acid) at 0 °C. The mixture was stirred at 0 °C until no more effervescence was observed (*ca.* 1 h) to give a solution of α,β -unsaturated acid chloride which was used directly in the next step.

Preparation of Amide-Tethered Cyclisation Precursors: General Procedure B

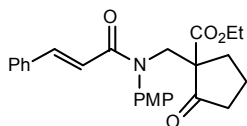


The appropriate α,β -unsaturated acid chloride (neat in the case of commercially available acid chlorides, or as a solution in CH_2Cl_2 prepared according to General Procedure A, 1.5 equiv) was added dropwise or portionwise to a vigorously stirred mixture of the appropriate aminoketone (1.0 equiv) in CH_2Cl_2 (1 mL/mmol of aminoketone) and saturated aqueous Na_2CO_3 solution (1 mL/mmol of aminoketone). The mixture was stirred at room temperature until TLC analysis showed the reaction to be complete. The reaction was partitioned between saturated aqueous NaHCO_3 solution and CH_2Cl_2 . The aqueous layer was separated and extracted with CH_2Cl_2 (x 3), and the combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclisation substrate.



1-[*N*-(*E*)-But-2-enoyl-*N*-(4-methoxyphenyl)aminomethyl]-2-oxocyclopentanecarboxylic acid ethyl ester (155l).

The title compound was prepared by General Procedure B from the amine **217** (295 mg, 1.00 mmol) and crotonoyl chloride (143 μ L, 1.50 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol) to give a pale brown oil (307 mg, 84%). IR (film) 2965, 1750 (C=O), 1719 (C=O), 1666 (C=O), 1629, 1510, 1445, 1289, 1249, 1029 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.09 (2H, d, J = 8.4 Hz, ArH), 6.92-6.82 (3H, m, ArH and $\text{CH}_3\text{CH=}$), 5.65 (1H, dd, J = 15.1, 1.7 Hz, $\text{CH}_3\text{CH=CH}$), 4.33 (1H, d, J = 13.9 Hz, CH_2N), 4.25 (1H, d, J = 13.9 Hz, CH_2N), 3.87-3.78 (1H, m, OCH_2CH_3), 3.83 (3H, s, OCH_3), 3.72-3.63 (1H, m, OCH_2CH_3), 2.55-1.97 (6H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.71 (3H, dd, J = 6.9, 1.7 Hz, $\text{CH}_3\text{CH=}$), 1.01 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (62.9 MHz, CDCl_3) δ 212.4 (C), 169.6 (C), 167.0 (C), 158.9 (C), 142.0 (CH), 134.3 (C), 129.5 (2 x CH), 122.2 (CH), 114.3 (2 x CH), 61.4 (CH_2), 60.8 (C), 55.4 (CH_3), 50.8 (CH_2), 38.1 (CH_2), 31.5 (CH_2), 19.5 (CH_2), 18.0 (CH_3), 13.7 (CH_3); HRMS (FAB) Exact mass calcd for $\text{C}_{20}\text{H}_{26}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 360.1806, found: 360.1809.



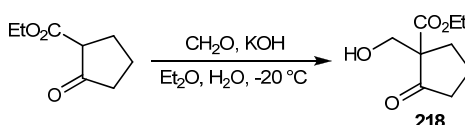
1-[*N*-(4-Methoxyphenyl)-*N*-((*E*)-3-phenylacryloyl)aminomethyl]-2-oxocyclopentanecarboxylic acid ethyl ester (155m).

The title compound was prepared by General Procedure B from the amine **217** (2.33 g, 8.00 mmol) and cinnamoyl chloride (2.04 g, 12.0 mmol) for a reaction time of 65 h and purified by column chromatography (10% EtOAc/petrol \rightarrow 30% EtOAc/petrol) to give a pale brown gum (2.19 g, 65%). IR (film) 2961, 1750 (C=O), 1720 (C=O), 1655 (C=O), 1616, 1510, 1249, 1029, 839, 806 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.62 (1H, d, J = 15.6 Hz, PhCH=), 7.29 (5H, br s, ArH), 7.16 (2H, app d, J = 7.8 Hz, ArH), 6.92 (2H, d, J = 9.1 Hz, ArH), 6.27 (1H, d, J = 15.6 Hz, PhCH=CH), 4.40 (1H, d, J = 13.9 Hz, CH_2N), 4.34 (1H, d, J = 13.9 Hz, CH_2N), 3.90-3.81 (1H, m, OCH_2CH_3), 3.85 (3H, s, OCH_3), 3.77- 3.67 (1H, m, OCH_2CH_3), 2.58-2.30 (3H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.24-2.13 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.09-1.98 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.04 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (90.6 MHz, CDCl_3) δ 212.5 (C), 169.6 (C), 167.1 (C), 159.0

(C), 142.5 (CH), 135.0 (C), 134.1 (C), 129.6 (2 x CH), 128.6 (2 x CH), 127.9 (2 x CH), 118.1 (CH), 114.4 (2 x CH), 61.5 (CH₂), 60.9 (C), 55.5 (CH₃), 51.0 (CH₂), 38.2 (CH₂), 31.6 (CH₂), 19.6 (CH₂), 13.7 (CH₃); LRMS (ES) Mass calcd for C₂₅H₂₈NO₅ [M+H]⁺: 422.2, found: 422.0.

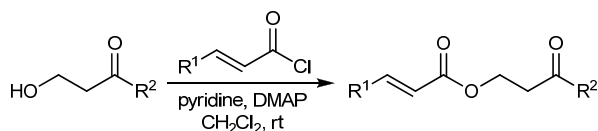
Preparation of Hydroxyketones

1-Hydroxymethyl-2-oxo-cyclopentanecarboxylic acid ethyl ester (**218**).⁵²



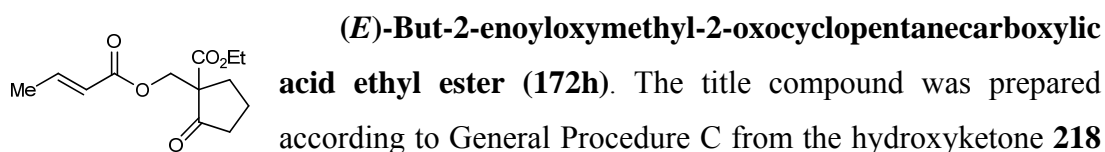
To a solution of 2-oxocyclopentanecarboxylate (0.60 mL, 4.00 mmol) and aqueous formaldehyde solution (37 % wt in H₂O, 1.80 mL, 24.0 mmol) in EtOH (20 mL) at –20 °C, was added KOH (673 mg, 12.0 mmol) portionwise over 5 min. The mixture was stirred at –20 °C for 0.5 h, and then poured into saturated aqueous NH₄Cl solution (20 mL). The mixture was extracted with CH₂Cl₂ (3 x 20 mL), and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (30% EtOAc/petrol) gave the alcohol **218** (432 mg, 58%) that displayed spectroscopic data consistent with those reported previously.⁵²

Preparation of Ester-Tethered Cyclisation Precursors: General Procedure C

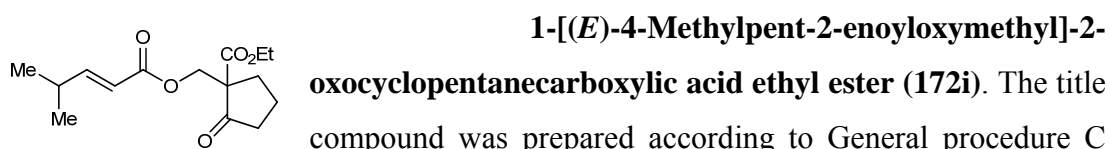


The appropriate α,β -unsaturated acid chloride (neat in the case of commercially available acid chlorides, or as a solution in CH₂Cl₂ prepared according to General Procedure A, 1.1 equiv) was added dropwise or portionwise to a vigorously stirred

mixture of the appropriate hydroxyketone (1.0 equiv), DMAP (0.05 equiv) and pyridine (4.0 equiv) in CH₂Cl₂ (1.0 M with respect to hydroxyketone) over 5 min *via* cannula, and the reaction was stirred at room temperature until TLC analysis showed the reaction to be complete. The reaction was partitioned between saturated aqueous NaHCO₃ solution and Et₂O. The organic layer was separated and washed with saturated aqueous NaHCO₃ solution (x 3), dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the cyclisation substrate.

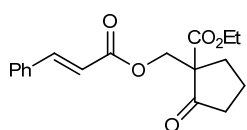


(152 mg, 0.80 mmol) and *trans*-crotonoyl chloride (0.12 mL, 1.20 mmol) for a reaction time of 22 h and purified by column chromatography (15% EtOAc/petrol) to give a colourless oil (96 mg, 46%). IR (film) 2979, 1755 (C=O), 1727 (C=O), 1657, 1446, 1294, 1261, 1234, 1175, 1029 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 6.93 (1H, dq, *J* = 15.5, 6.9 Hz, =CH), 5.79 (1H, dq, *J* = 15.5, 1.7 Hz, =CH), 4.49 (1H, d, *J* = 11.1 Hz, CCH₂O), 4.40 (1H, d, *J* = 11.1 Hz, CCH₂O), 4.17 (2H, q, *J* = 7.1 Hz, OCH₂CH₃), 2.55-1.93 (6H, m, CH₂CH₂CH₂), 1.86 (3H, dd, *J* = 6.9, 1.7 Hz, CH₃CH=), 1.24 (3H, t, *J* = 7.1 Hz, OCH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 212.4 (C), 169.4 (C), 165.8 (C), 145.5 (CH), 122.0 (CH), 64.2 (CH₂), 61.7 (CH₂), 59.6 (C), 38.3 (CH₂), 31.1 (CH₂), 19.7 (CH₂), 18.0 (CH₃), 14.0 (CH₃); HRMS (ES) Exact mass calcd for C₁₃H₁₉O₅ [M+H]⁺: 255.1227, found: 255.1224.



from the hydroxyketone **218** (500 mg, 2.70 mmol) and the acid chloride (prepared according to General Procedure A) derived from 4-methylpent-2-enoic acid (462 mg, 4.10 mmol) for a reaction time of 43 h and purified by column chromatography (15% EtOAc/petrol) to give a colourless oil (306 mg, 40%). IR (film) 2968, 1754 (C=O),

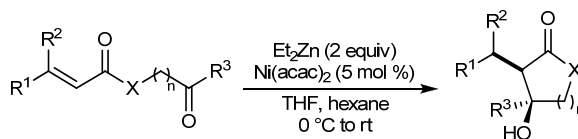
1727 (C=O), 1653, 1458, 1366, 1262, 1155, 1022, 860 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 6.94 (1H, dd, J = 15.7, 6.6 Hz, =CH), 5.73 (1H, dd, J = 15.7, 1.5 Hz, =CH), 4.52 (1H, d, J = 11.2 Hz, CCH_2O), 4.44 (1H, d, J = 11.2 Hz, CCH_2O), 4.20 (2H, q, J = 7.1 Hz, OCH_2CH_3), 2.56-2.41 (3H, m), 2.38-2.28 (1H, m) and 2.20-1.98 (3H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$ and $(\text{CH}_3)_2\text{CH}$), 1.27 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.06 (6H, d, J = 6.8 Hz, $(\text{CH}_3)_2\text{CH}$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 212.5 (C), 169.3 (C), 166.4 (C), 156.6 (CH), 117.8 (CH), 64.3 (CH_2), 61.8 (CH_2), 59.7 (C), 38.4 (CH_2), 31.1 (CH_2), 31.0 (CH), 21.1 (2 x CH_3), 19.8 (CH_2), 14.0 (CH_3).



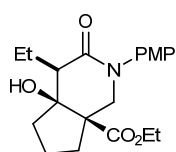
2-Oxo-1-[(*E*)-3-phenylacryloyl]oxymethylcyclopentanecarboxylic acid ethyl ester (172j). The title compound was prepared according

to General Procedure C from the hydroxyketone **218** (488 mg, 2.60 mmol) and cinnamoyl chloride (655 mg, 3.90 mmol) for a reaction time of 60 h and purified by column chromatography (10% EtOAc/petrol) to give a colourless oil (431 mg, 52%). IR (film) 2979, 1754 (C=O), 1722 (C=O), 1636, 1450, 1309, 1234, 1202, 1154, 1020 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.68 (1H, d, J = 16.0 Hz, =CH), 7.54-7.51 (2H, m, ArH), 7.42-7.39 (3H, m, ArH), 6.40 (1H, d, J = 16.0 Hz, =CH), 4.62 (1H, d, J = 11.2 Hz, CCH_2O), 4.51 (1H, d, J = 11.2 Hz, CCH_2O), 4.22 (2H, q, J = 7.1 Hz, OCH_2CH_3), 2.59-2.48 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.41-2.32 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.24-2.01 (3H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.28 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (62.9 MHz, CDCl_3) δ 212.4 (C), 169.2 (C), 166.4 (C), 145.6 (CH), 134.1 (C), 130.5 (CH), 128.9 (2 x CH), 128.1 (2 x CH), 117.2 (CH), 64.5 (CH_2), 61.8 (CH_2), 59.7 (C), 38.4 (CH_2), 31.1 (CH_2), 19.7 (CH_2), 14.0 (CH_3); HRMS (ES) Exact mass calcd for $\text{C}_{18}\text{H}_{24}\text{NO}_5$ $[\text{M}+\text{NH}_4]^+$: 334.1649, found: 334.1651.

Nickel-Catalyzed Reductive Aldol Cyclisations Using Ni(acac)₂: General Procedure D



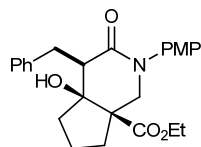
A solution of the substrate (0.20 mmol) and Ni(acac)₂ (2.7 mg, 0.01 mmol) in THF (1.5 mL) was stirred at room temperature for 15 min. The mixture was cooled to 0 °C and Et₂Zn (1 M solution in hexane, 0.40 mL, 0.40 mmol) was then added rapidly in one portion. The reaction was stirred at 0 °C for 1 h and then at room temperature until complete consumption of starting material as observed by TLC analysis. The reaction was quenched carefully by the addition saturated aqueous NH₄Cl solution (20 mL). The mixture was extracted with CH₂Cl₂ (3 x 15 mL) and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclised product.



(±)-(1R,5R,6S)-1-Carbethoxy-5-ethyl-6-hydroxy-3-(4-methoxyphenyl)-3-azabicyclo[4.3.0]nonan-4-one (156l). The title compound was prepared according to General Procedure D from **155l** (72 mg, 0.20 mmol) for a reaction time of 22.5 h and purified by

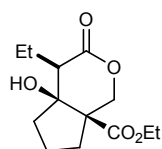
column chromatography (40% EtOAc/petrol→50% EtOAc/petrol) to give a colourless oil (45 mg, 62%). IR (film) 3431 (OH), 2965, 1725 (C=O), 1666 (C=O), 1512, 1288, 1247, 1101, 1033, 836 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.20 (2H, dm, *J* = 9.1 Hz, ArH), 6.87 (2H, dm, *J* = 9.1 Hz, ArH), 4.16 (1H, d, *J* = 13.6 Hz, CH₂N), 4.10 (2H, q, *J* = 7.2 Hz, OCH₂CH₃), 3.79 (3H, s, OCH₃), 3.61 (1H, d, *J* = 13.6 Hz, CH₂N), 3.27 (1H, br s, OH), 2.42-2.34 (2H, m), 2.17-2.03 (2H, m), 2.00-1.91 (2H, m) and 1.78-1.62 (3H, m, CH₃CH₂CH and CH₂CH₂CH₂), 1.10 (3H, t, *J* = 7.2 Hz, OCH₂CH₃), 1.08 (3H, t, *J* = 7.4 Hz, CH₃CH₂CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 174.6 (C), 170.9 (C), 157.4 (C), 135.7 (C), 126.3 (2 x CH), 113.8 (2 x CH), 85.8 (C), 61.4 (CH₂), 57.8 (C), 55.4 (CH₃), 54.6 (CH₂), 53.2 (CH), 41.8 (CH₂), 36.6

(CH₂), 23.5 (CH₂), 18.3 (CH₂), 14.1 (CH₃), 13.9 (CH₃); HRMS (FAB) Exact mass calcd for C₂₀H₂₈NO₅ [M+H]⁺: 362.1963, found: 348.1962.



(±)-(1R,5R,6S)-5-Benzyl-1-carbethoxy-6-hydroxy-3-(4-methoxyphenyl)-3-azabicyclo[4.3.0]nonan-4-one (156m). The title compound was prepared according to General Procedure D from **155m** (84 mg, 0.20 mmol) for a reaction time of 16.5 h and

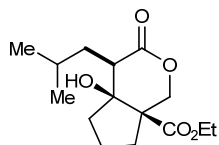
purified by column chromatography (40% EtOAc/petrol) to give a colourless oil (42 mg, 50%). IR (film) 3438 (OH), 2962, 1724 (C=O), 1671 (C=O), 1512, 1465, 1287, 1247, 1115, 832 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.39-7.36 (2H, m, ArH), 7.29-7.24 (2H, m, ArH), 7.21-7.15 (1H, m, ArH), 7.18 (2H, dm, *J* = 9.1 Hz, ArH), 6.86 (2H, dm, *J* = 9.1 Hz, ArH), 4.11 (2H, q, *J* = 7.1 Hz, OCH₂CH₃), 4.11 (1H, d, *J* = 13.7 Hz, CH₂N), 3.79 (3H, s, OCH₃), 3.63 (1H, d, *J* = 13.7 Hz, CH₂N), 3.59 (1H, dd, *J* = 14.4, 8.1 Hz, CH₂CH), 3.51 (1H, s, OH), 2.96 (1H, dd, *J* = 14.4, 2.8 Hz, CH₂CH), 2.78 (1H, dd, *J* = 8.1, 2.8 Hz, CH₂CH), 2.40-2.23 (2H, m, CH₂CH₂CH), 2.05-1.91 (2H, m, CH₂CH₂CH₂), 1.73-1.62 (2H, m, CH₂CH₂CH₂), 1.08 (3H, t, *J* = 7.1 Hz, OCH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 174.7 (C), 170.3 (C), 157.3 (C), 142.1 (C), 135.6 (C), 129.3 (2 x CH), 128.2 (2 x CH), 126.2 (2 x CH), 125.8 (CH), 113.8 (2 x CH), 86.4 (C), 61.5 (CH₂), 58.0 (C), 55.4 (CH₃), 54.4 (CH₂), 53.6 (CH), 41.8 (CH₂), 36.4 (CH₂), 31.0 (CH₂), 23.4 (CH₂), 13.8 (CH₃); HRMS (FAB) Exact mass calcd for C₂₅H₃₀NO₅ [M+H]⁺: 424.2119, found: 424.2129.



(±)-(1R,5R,6S)-1-Carbethoxy-5-ethyl-6-hydroxy-3-oxabicyclo[4.3.0]nonan-4-one (173h) . The title compound was prepared according to General Procedure D from **172h** (51 mg, 0.20

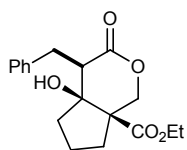
mmol) for a reaction time of 3.5 h and purified by column chromatography (30% EtOAc/petrol) to give a colourless oil (45 mg, 88%). IR (film) 3489 (OH), 2972, 1734 (C=O), 1467, 1329, 1305, 1270, 1186, 1134, 1061 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 4.68 (1H, d, *J* = 12.1 Hz, CCH₂O), 4.22 (2H, q, *J* = 7.2 Hz, OCH₂CH₃), 3.97 (1H, d, *J* = 12.1 Hz, CCH₂O), 3.62 (1H, s, OH), 2.37 (1H, dd, *J* = 9.3, 2.7 Hz, CH₂CH), 2.33-2.21 (1H, m), 2.16-1.88 (4H, m), and 1.73-1.58 (3H, m, CH₂CH₂CH₂

and CH_2CH), 1.28 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 1.05 (3H, t, $J = 7.4$ Hz, $\text{CH}_3\text{CH}_2\text{CH}$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 174.1 (C), 172.5 (C), 85.0 (C), 69.2 (CH_2), 61.9 (CH_2), 56.5 (C), 50.4 (CH), 41.5 (CH_2), 35.0 (CH_2), 23.4 (CH_2), 18.1 (CH_2), 14.0 (CH_3), 13.6 (CH_3); HRMS (ES) Exact mass calcd for $\text{C}_{13}\text{H}_{24}\text{NO}_5$ $[\text{M}+\text{NH}_4]^+$: 274.1649, found: 274.1647.



(±)-(1R,5R,6S)-5-Iso-butyl-1-carbethoxy-6-hydroxy-3-oxabicyclo[4.3.0]nonan-4-one (173i). The title compound was

prepared according to General Procedure D from **172i** (56 mg, 0.20 mmol) for a reaction time of 21 h and purified by column chromatography (10% EtOAc/petrol→30% EtOAc/petrol) to give a colourless oil (42 mg, 74%). IR (film) 3489 (OH), 2957, 2871, 1740 ($\text{C}=\text{O}$), 1469, 1369, 1302, 1249, 1175, 1118 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 4.72 (1H, d, $J = 12.1$ Hz, CCH_2O), 4.24 (2H, q, $J = 7.1$ Hz, OCH_2CH_3), 4.00 (1H, d, $J = 12.1$ Hz, CCH_2O), 3.58 (1H, d, $J = 1.0$ Hz, OH), 2.52 (1H, dd, $J = 9.2, 1.6$ Hz, $\text{CHC}=\text{O}$), 2.33-2.24 (1H, m), 2.13-2.04 (2H, m), 1.99-1.90 (2H, m), 1.77-1.61 (3H, m) and 1.37-1.30 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$ and $(\text{CH}_3)_2\text{CHCH}_2$), 1.30 (3H, t, $J = 7.1$ Hz, OCH_2CH_3), 0.98 (3H, d, $J = 6.6$ Hz, $(\text{CH}_3)_2\text{CH}$), 0.88 (3H, d, $J = 6.6$ Hz, $(\text{CH}_3)_2\text{CH}$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 174.1 (C), 172.7 (C), 85.2 (C), 69.2 (CH_2), 62.0 (CH_2), 56.4 (C), 46.1 (CH), 41.5 (CH_2), 35.1 (CH_2), 33.7 (CH_2), 26.5 (CH), 23.4 (CH_3), 23.3 (CH_2), 21.6 (CH_3), 14.0 (CH_3).



(±)-(1R,5R,6S)-5-Benzyl-1-carbethoxy-6-hydroxy-3-oxabicyclo[4.3.0]nonan-4-one (173j). The title compound was

prepared according to General Procedure D from **172j** (63 mg, 0.20 mmol) for a reaction time of 2 h and purified by column chromatography (30% EtOAc/petrol) to give a colourless oil (47 mg, 73%). IR (film) 3481 (OH), 2967, 1739 ($\text{C}=\text{O}$), 1454, 1394, 1368, 1305, 1240, 1126, 1043 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.34-7.26 (4H, m, ArH), 7.22-7.18 (1H, m, ArH), 4.69 (1H, d, $J = 12.1$ Hz, CCH_2O), 4.26 (2H, q, $J = 7.1$ Hz, OCH_2CH_3), 3.95 (1H, d, $J = 12.1$ Hz, CCH_2O), 3.90 (1H, d, $J = 0.9$ Hz, OH), 3.41 (1H, dd, $J = 14.6, 8.0$ Hz, CH_2CH), 2.98 (1H, dd,

$J = 14.6, 3.4$ Hz, CH_2CH), 2.79 (1H, dd, $J = 8.0, 3.4$ Hz, CH_2CH), 2.32-2.12 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.98-1.89 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.69-1.58 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.32 (3H, t, $J = 7.1$ Hz, OCH_2CH_3); ^{13}C NMR (62.9 MHz, CDCl_3) δ 174.2 (C), 172.1 (C), 140.8 (C), 129.2 (2 x CH), 128.4 (2 x CH), 126.2 (CH), 85.2 (C), 69.2 (CH_2), 62.2 (CH_2), 56.6 (C), 51.1 (CH), 41.8 (CH_2), 35.0 (CH_2), 30.9 (CH_2), 23.4 (CH_2), 14.0 (CH_3); HRMS (EI) Exact mass calcd for $\text{C}_{18}\text{H}_{22}\text{O}_5$ $[\text{M}]^+$: 318.1462, found: 318.1463.

Nickel-Catalyzed Reductive Aldol Cyclisations Using $\text{Ni}(\text{COD})_2$: General Procedure E

In a glovebox, an oven-dried vial was charged with $\text{Ni}(\text{COD})_2$ (2.8 mg, 0.01 mmol) and a stirrer bar, and capped with a septum. The vial was removed from the glovebox and placed under a positive pressure of nitrogen. A solution of the substrate (0.20 mmol) in THF (0.8 mL + 0.7 mL rinse) was added *via* cannula, and the resulting mixture was stirred for 15 min, cooled to 0 °C, before Et_2Zn (1 M solution in hexane, 0.40 mL, 0.40 mmol) was added rapidly in one portion. The reaction was stirred at 0 °C for 1 h and then at room temperature for 16 h. Workup was carried out according to one of the procedures described below.

Workup A

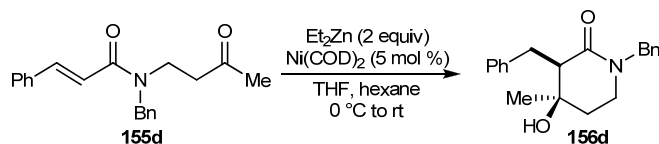
The reaction mixture was filtered through a short plug of SiO_2 (*ca.* 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclised product.

Workup B

The reaction was quenched carefully by the addition of 1 M HCl (1 mL), and the mixture was stirred for 1 h before being diluted with saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 15 mL) and the

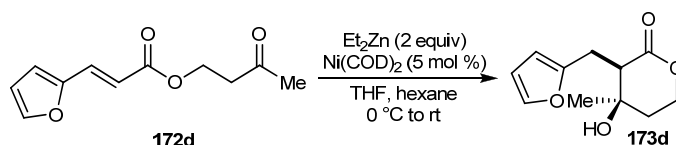
combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclised product.

Cyclisation of **155d**



General Procedure E was followed using **155d** (61 mg, 0.20 mmol) and the reaction mixture was subjected to Workup A. ^1H NMR analysis of the unpurified reaction mixture showed that **156d** had been formed in >90% conversion.

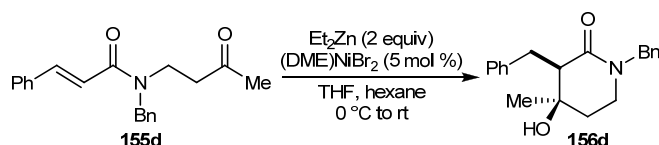
Cyclisation of **172d**



General Procedure I was followed using **172d** (42 mg, 0.20 mmol) and the reaction mixture was subjected to Workup B. ^1H NMR analysis of the unpurified reaction mixture showed that **173d** had been formed in only <20% conversion.

Nickel-Catalyzed Reductive Aldol Cyclisations Using $(\text{DME})\text{NiBr}_2$

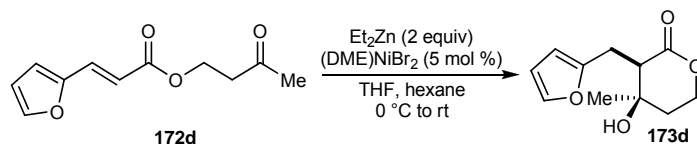
Cyclisation of **155d**



Using $(\text{DME})\text{NiBr}_2$ (3.1 mg, 0.01 mmol) as precatalyst in place of $\text{Ni}(\text{acac})_2$, General Procedure D was followed using **155d** (61 mg, 0.20 mmol) for a reaction time of 20

h followed by Workup A. ^1H NMR analysis of the unpurified reaction mixture showed that **156d** had been formed in >90% conversion.

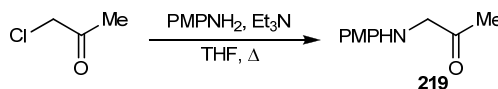
Cyclisation of **172d**



Using (DME)NiBr₂ (3.1 mg, 0.01 mmol) as precatalyst in place of Ni(acac)₂, General Procedure D was followed using **172d** (42 mg, 0.20 mmol) for a reaction time of 20 h followed by Workup B. ^1H NMR analysis of the unpurified reaction mixture showed that **173d** had been formed in >90% conversion.

Preparation and Cyclisation of Substrate **191**

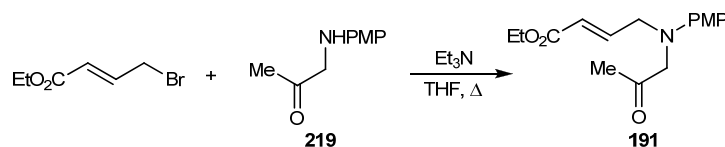
1-(4-Methoxyphenyl)aminopropanone (**219**)



A solution of *p*-anisidine (5.00 g, 40.6 mmol), chloroacetone (3.56 mL, 44.7 mmol) and Et₃N (11.3 mL, 81.2 mmol) in THF (100 mL) was heated at reflux for 24 h. The reaction mixture was cooled to room temperature before the addition of brine (25 mL) and water (25 mL). The aqueous layer was separated and extracted with EtOAc (2 x 30 mL), and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (40% EtOAc/petrol→50% EtOAc/petrol) gave the *aminoketone* **219** as a yellow/orange crystalline solid (4.60 g, 68%). m.p. 70-71 °C; IR (CHCl₃) 3397 (NH), 2961, 2839, 1715 (C=O), 1511, 1436, 1345, 1254, 1036, 821 cm⁻¹; ^1H NMR (360 MHz, CDCl₃) δ 6.79 (2H, dm, J = 9.0 Hz, ArH), 6.56 (2H, dm, J = 9.0 Hz, ArH), 4.31 (1H, bs, NH), 3.95 (2H, s, CH₂N), 3.74 (3H, s, OCH₃), 2.23 (3H, s, CH₃C=O); ^{13}C NMR (62.9 MHz, CDCl₃) δ 204.5 (C), 152.2 (C), 141.2 (C), 114.9 (2 x CH), 113.9 (2 x

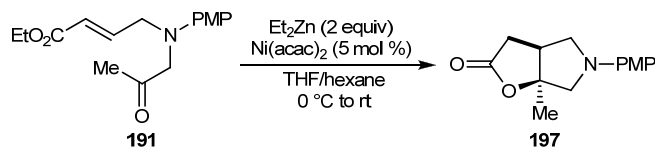
CH), 55.7 (CH₃), 55.1 (CH₂), 27.3 (CH₃); HRMS (FAB) Exact mass calcd for C₂₁H₂₄NO₃ [M+H]⁺: 180.1020, found: 180.1032.

(E)-Ethyl 4-(4-methoxyphenyl-2-oxopropylamino)but-2-enoate (191)



A solution of amine **219** (895 mg, 5.00 mmol), ethyl 4-bromocrotonate (75%, 1.38 mL, 7.52 mmol) and Et₃N (1.39 mL, 10.0 mmol) in THF (60 mL) was heated to reflux for 24 h. The mixture was cooled to room temperature, quenched with saturated aqueous NH₄Cl solution (20 mL), and extracted with CH₂Cl₂ (2 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (20% Et₂O/hexane→80% Et₂O/hexane) gave the *allyl amine* **191** (1.06 g, 73%) as an orange oil. IR (film) 2983, 2936, 2905, 2833, 1716 (C=O), 1657 (C=O), 1515, 1273, 1243, 1163 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 6.95 (1H, dt, *J* = 15.7, 4.5 Hz, O=CCH=CH), 6.78 (2H, dm, *J* = 9.2 Hz, ArH), 6.51 (2H, dm, *J* = 9.2 Hz, ArH), 5.96 (1H, d, *J* = 15.7 Hz, O=CCH=), 4.17 (2H, q, *J* = 7.1 Hz, OCH₂CH₃), 4.08 (2H, dd, *J* = 4.5, 1.6 Hz, =CHCH₂N), 3.97 (2H, s, CH₂C=O), 3.73 (3H, s, OCH₃), 2.14 (3H, s, CH₃C=O), 1.26 (3H, t, *J* = 7.1 Hz, OCH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 207.5 (C), 166.0 (C), 152.4 (C), 144.2 (CH), 142.0 (C), 122.3 (CH), 114.8 (2 x CH), 114.1 (2 x CH), 61.6 (CH₂), 60.4 (CH₂), 55.6 (CH₃), 53.6 (CH₂), 27.0 (CH₃), 14.1 (CH₃). HRMS (EI) Exact mass calcd for C₁₆H₂₁NO₄ [M]⁺: 291.1465, found: 291.1466.

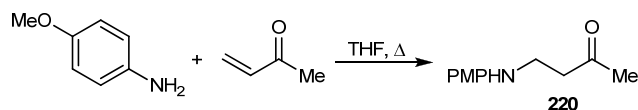
(±)-(3a*S*,6a*S*)-5-(4-Methoxyphenyl)-6a-methyl-hexahydrofuro[2,3-*c*]pyrrol-2-one (197)



The title compound was prepared according to General Procedure D from **191** (58 mg, 0.20 mmol) for a reaction time of 20 h followed by Workup A and purification by column chromatography (hexane→40% EtOAc/hexane) to give a brown oil (28 mg, 56%). IR (film) 2933, 2833, 1770 (C=O), 1515, 1244, 1178, 1037, 962, 819, 772 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.85 (2H, dm, $J = 9.1$ Hz, ArH), 6.62, (2H, dm, $J = 9.1$ Hz, ArH), 3.78 (1H, d, $J = 10.8$ Hz, CH_2N), 3.77 (3H, s, OCH_3), 3.40 (1H, dd, $J = 9.7, 7.5$ Hz, CH_2N), 3.31 (1H, dd, $J = 9.7, 3.8$ Hz, CH_2N), 3.10 (1H, d, $J = 10.8$ Hz, CH_2N), 2.98 (1H, dd, $J = 18.1, 9.6$ Hz, $\text{CH}_2\text{C}=\text{O}$), 2.85-2.80 (1H, m, CHCH_2N), 2.59 (1H, dd, $J = 18.1, 3.3$ Hz, $\text{CH}_2\text{C}=\text{O}$), 1.62 (3H, s, CH_3CO); ^{13}C NMR (62.9 MHz, CDCl_3) δ 175.7 (C), 152.6 (C), 142.2 (C), 115.0 (2 x CH), 114.8 (2 x CH), 91.8 (C), 60.9 (CH_2), 56.0 (CH_2), 55.7 (CH_3), 43.4 (CH), 35.9 (CH_2), 24.2 (CH_3); HRMS (EI) Exact mass calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_3$ $[\text{M}]^+$: 247.1203, found: 247.1201.

Preparation and Partial Cyclisation/Isomerisation Studies of Z-205

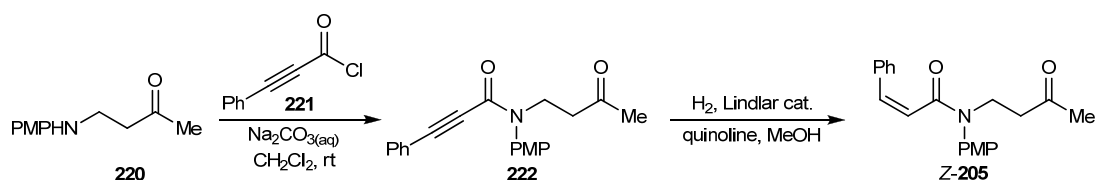
4-(4-Methoxyphenylamino)butan-2-one (220)



A solution of methyl vinyl ketone (7.0 mL, 85 mmol) and *p*-anisidine (8.86 g, 71.2 mmol) in THF (1.0 M with respect to *p*-anisidine) was heated at reflux for 24 h. The mixture was cooled to room temperature and washed with brine. The aqueous layer was extracted with EtOAc (x 2), and the combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (30% EtOAc/petrol→50% EtOAc/petrol) afforded the β -

aminoketone **220** (13.6 g, 99%), which was judged to be *ca.* 90% pure by ^1H NMR spectroscopy. IR (film) 3379 (NH), 2935, 1711 (C=O), 1513, 1465, 1361, 1237, 1169, 1036, 822 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 6.78 (2H, d, $J = 9.0$ Hz, ArH), 6.58 (2H, d, $J = 9.0$ Hz, ArH), 3.74 (3H, s, OCH_3), 3.53 (1H, bs, NH), 3.34 (2H, t, $J = 6.2$ Hz, CH_2N), 2.71 (2H, t, $J = 6.2$ Hz, $\text{CH}_2\text{CH}_2\text{N}$), 2.15 (3H, s, $\text{CH}_3\text{C}=\text{O}$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 208.2 (C), 152.1 (C), 141.7 (C), 114.7 (2 x CH), 114.4 (2 x CH), 55.6 (CH_3), 42.5 (CH_2), 39.3 (CH_2), 30.2 (CH_3); LRMS (ES) Mass calculated for $\text{C}_{11}\text{H}_{16}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 194.1, found: 194.0.

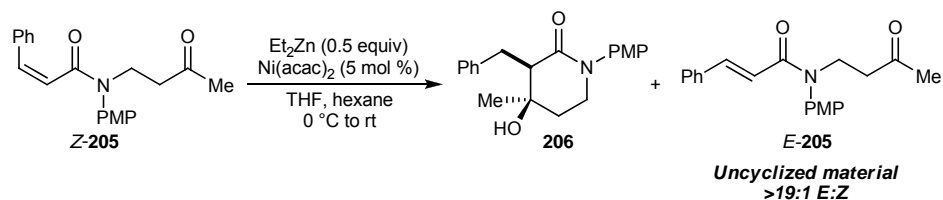
***N*-(4-Methoxy)-*N*-(3-oxobutyl)-3-phenylpropynamide (**222**) and *N*-(4-methoxy)-*N*-(3-oxobutyl)-(Z)-3-phenylpropenamide (**Z-205**)**



The alkyne **222** was prepared according to General Procedure B using amine **220** (1.00 g, 5.17 mmol) and the acid chloride **221** (prepared according to General Procedure A) derived from phenylpropionic acid (1.13 g, 7.76 mmol) for a reaction time of 17 h, followed by column chromatography (hexane→60% EtOAc/hexane) and recrystallisation from EtOAc/hexane to give a pale white solid (886 mg, 53%). m.p. 79-81 °C; IR (CHCl_3) 2359, 2215 ($\text{C}\equiv\text{C}$), 1714 (C=O), 1635 (C=O), 1510, 1395, 1320, 1249, 1167, 1029 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.35-7.30 (1H, m, ArH), 7.26-7.20 (4H, m, ArH), 7.17-7.13 (2H, m, ArH), 6.95 (2H, dm, $J = 8.9$ Hz, ArH), 4.04 (2H, t, $J = 7.4$ Hz, CH_2N), 3.85 (3H, s, OCH_3), 2.78 (2H, t, $J = 7.4$ Hz, $\text{CH}_2\text{CH}_2\text{N}$), 2.14 (3H, s, $\text{CH}_3\text{C}=\text{O}$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 206.4 (C), 159.3 (C), 154.5 (C), 134.3 (C), 132.4 (2 x CH), 129.9 (CH), 129.5 (2 x CH), 128.3 (2 x CH), 120.3 (C), 114.3 (2 x CH), 91.1 (C), 82.5 (C), 55.5 (CH_3), 44.1 (CH_2), 41.2 (CH_2), 30.0 (CH_3); HRMS (EI) Exact mass calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_3$ $[\text{M}]^+$: 321.1360, found 321.1358.

A vial containing a suspension of Lindlar catalyst (5 % Pd on CaCO₃, poisoned with Pb, 66 mg, 0.03 mmol), quinoline (8 μ L, 0.06 mmol), and the alkyne **222** (50 mg, 0.16 mmol) in MeOH (0.5 mL) was purged with H₂ using a balloon, and then stirred vigorously under the H₂ atmosphere for 15 min. The mixture was filtered through a short plug of SiO₂ (*ca.* 2 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 30 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (hexane \rightarrow 50% EtOAc/hexane) gave the *alkene* **Z-205** (41 mg, 79 %) as a pale brown oil. IR (film) 2936, 1713 (C=O), 1652 (C=O), 1512, 1371, 1248, 1170, 1030, 834, 698 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.42-7.29 (5H, m, ArH), 6.86 (2H, dm, *J* = 9.2 Hz, ArH), 6.80 (2H, dm, *J* = 9.2 Hz, ArH), 6.37 (1H, d, *J* = 12.6 Hz, =CH), 5.76 (1H, d, *J* = 12.6 Hz, =CH), 3.98 (2H, t, *J* = 7.4 Hz, CH₂N), 3.78 (3H, s, OCH₃), 2.74 (2H, t, *J* = 7.4 Hz, CH₂N), 2.14 (3H, s, CH₃C=O); ¹³C NMR (62.9 MHz, CDCl₃) δ 206.8 (C), 168.0 (C), 158.8 (C), 135.5 (C), 135.0 (CH), 134.4 (C), 128.9 (2 x CH), 128.6 (2 x CH), 128.3 (CH), 128.1 (2 x CH), 123.8 (CH), 114.3 (2 x CH), 55.4 (CH₃), 44.4 (CH₂), 41.3 (CH₂), 29.9 (CH₃).

Isomerisation Studies of **Z-205**



A solution of the substrate (0.20 mmol) and Ni(acac)₂ (2.7 mg, 0.01 mmol) in THF (1.5 mL) was stirred at room temperature for 15 min. The mixture was cooled to 0 °C and Et₂Zn (1 M solution in hexane, 0.10 mL, 0.10 mmol) was then added rapidly in one portion. The reaction was stirred at 0 °C for 1 h and then at room temperature for 17 h. After Workup A, the ¹H NMR spectrum of the unpurified reaction mixture showed the presence of a 1:1.6 mixture of **206** and **E-205**, compounds that have been described previously.⁴⁰

3. The Chemistry of Cyclopropenes

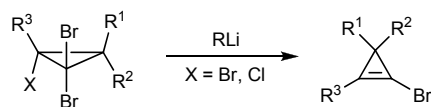
3.1 Introduction

Three-membered carbocycles are extremely important and versatile building blocks in organic chemistry and are present in many biologically important molecules.⁵³ Cyclopropenes, in particular, are of interest because the highly strained nature of their structure allows them to undergo transformations that are thermodynamically unfavourable for other olefins.⁵⁴ Furthermore, the significant conformational constraints imposed on cyclopropenes makes them ideal models for the design and optimisation of novel diastereo- and enantioselective transformations. As a consequence, cyclopropenes have attracted much interest from synthetic chemists for many years.^{54,55}

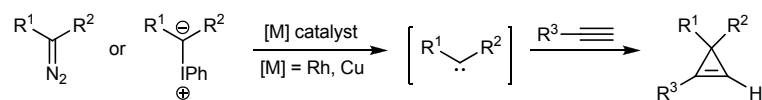
3.1.1 Synthesis of Cyclopropenes: An Overview

Since first being reported over 100 years ago, numerous synthetic approaches have been developed to access cyclopropene and its derivatives. Some examples of the key synthetic approaches are summarised in Scheme 3.1 and these include: (a) 1,2-elimination from cyclopropane precursors possessing good leaving-groups;⁵⁶ (b) [2+1] cycloadditions of carbenoids generated from diazo compounds⁵⁷ or iodonium ylides⁵⁸ to alkynes; (c) cycloisomerisation of vinylcarbenes generated *in situ* from tosyl hydrazone,⁵⁹ diazo alkenes,⁶⁰ vinyl diazirines,⁶¹ or allyl halides;⁶² and (d) cascade 1,3/1,2-elimination from 1,3-dihalopropanes.⁶³ These and other less common approaches to the synthesis of cyclopropenes have been comprehensively reviewed by Baird⁶⁴ and Hopf.⁶⁵

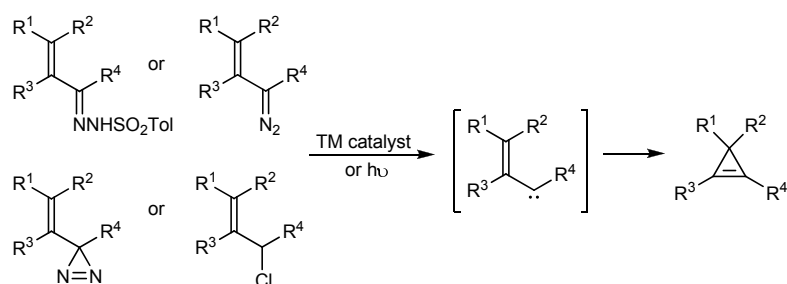
(a) 1,2-Elimination from 1,2,2-trihalocyclopropanes



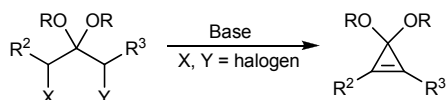
(b) [2 + 1] Cycloaddition of metal carbenoids to alkynes



(c) Cycloisomerisation of vinylcarbenes

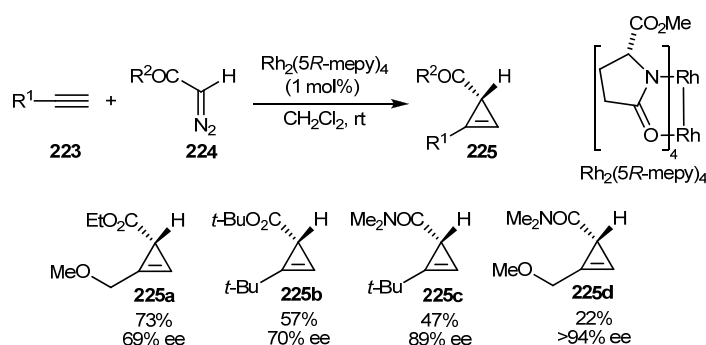


(d) Cascade 1,3/1,2-eliminations



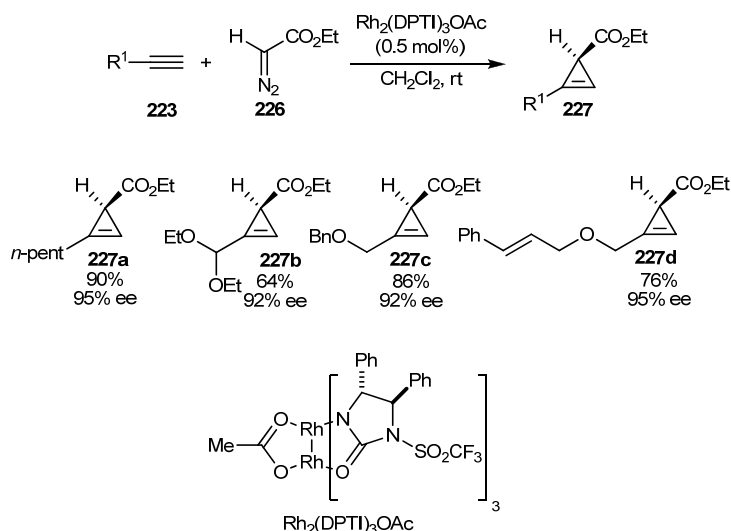
Scheme 3.1 Synthetic Approaches to Cyclopropenes

In recent years, focus has moved to the synthesis of chiral non-racemic cyclopropenes as a means to access optically active cyclopropanes.^{54g} The first asymmetric synthesis of chiral cyclopropene derivatives was jointly reported by Doyle, Müller, and co-workers in 1992.⁶⁶ Using substoichiometric quantities of $Rh_2(5R\text{-mepy})_4$, a range of 1,3-disubstituted cyclopropenes were synthesised in moderate to excellent enantioselectivities, from the corresponding diazo compounds and terminal alkynes (Scheme 3.2).



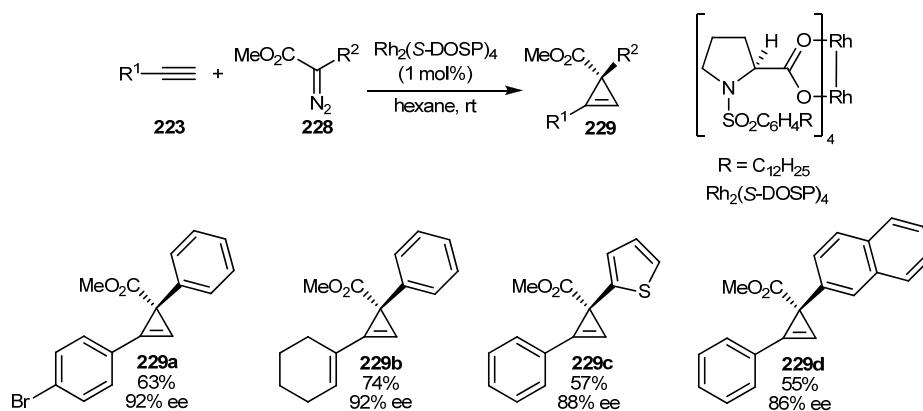
Scheme 3.2 Examples of Asymmetric Cyclopropanation using $\text{Rh}_2(5R\text{-mepy})_4$

Corey and co-workers extended the scope of this methodology to a broader range of terminal alkynes by using $\text{Rh}_2(\text{DPTI})_3\text{OAc}$ as a catalyst (Scheme 3.3).^{67, 68}



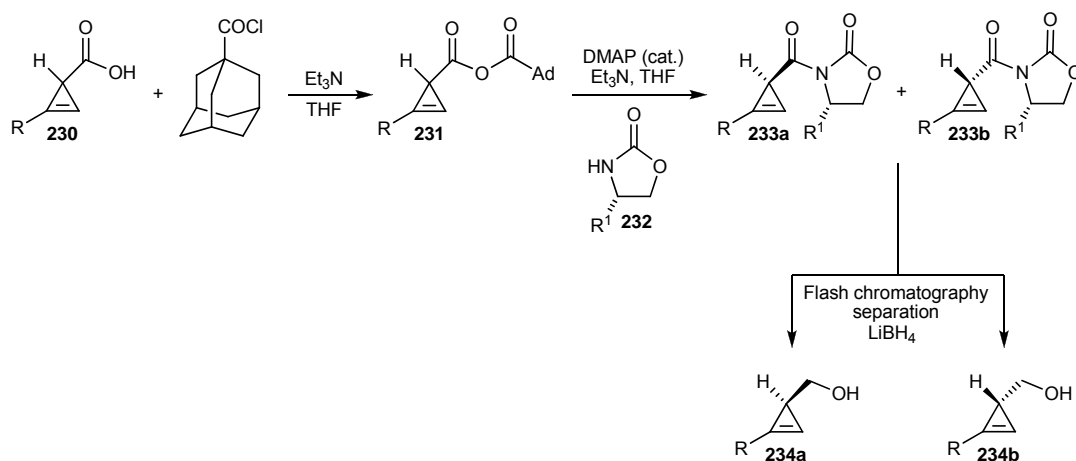
Scheme 3.3 Examples of Asymmetric Cyclopropanation using $\text{Rh}_2(\text{DPTI})_3\text{OAc}$

In 2004, Davies and Lee reported the first examples of the synthesis of optically active cyclopropanes containing a quaternary C3 centre.⁶⁹ It was demonstrated that a variety of terminal alkynes and aryldiazoacetates underwent enantioselective cyclopropanation in the presence of substoichiometric quantities of $\text{Rh}_2(\text{DOSP})_4$ to yield the corresponding cyclopropanes with good enantioselectivities (Scheme 3.4).



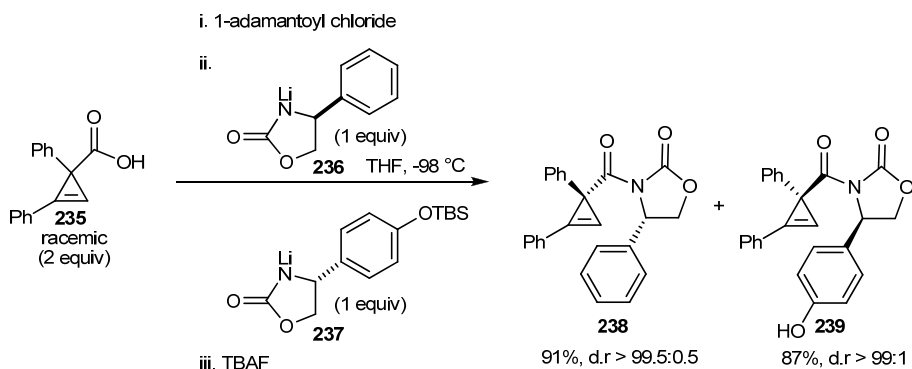
Scheme 3.4 Examples of Asymmetric Cyclopropanation using $\text{Rh}_2(\text{DOSP})_4$

Optically active cyclopropenes can also be accessed by chiral resolution. For example, Fox and co-workers have reported an efficient method for resolving cyclopropene carboxylic acids based on the formation of diastereomeric *N*-acyloxazolidinones (Scheme 3.5).⁷⁰ Several commercially available oxazolidinones were used and the best auxiliaries, in terms of the resolving ability, were those from (*S*)-phenylalaninol, (*S*)-phenylglycinol and (1*R*, 2*S*)-1-amino-2-indanol. Separation was carried out using simple flash chromatography to provide diastereomerically pure material, which on reduction with LiBH_4 led to the corresponding enantiomerically pure alcohols.

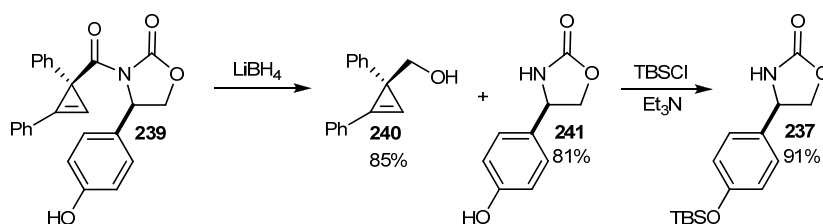


Scheme 3.5 Optical Resolution of Cyclopropenyl Carbinols

Interestingly, when DMAP is excluded from the reaction, a kinetic resolution is observed. To further increase the efficiency of this resolution, a parallel kinetic resolution of cyclopropenes was also developed by Fox and co-workers.⁷¹ The principle of this process is that quasienantiomers, which have very similar reactivities, give products whose chromatographic properties diverge upon the addition of fluoride. Thus, using commercially available oxazolidinone *S*-**236** and its quasienantiomer *R*-**237** a variety of cyclopropene carboxylic acids, that have all-carbon quaternary centres, underwent parallel kinetic resolution to provide the corresponding diastereomers with excellent selectivity (Scheme 3.6). Cleavage of the oxazolidinone with LiBH₄ gives access to the enantiomerically pure 3-hydroxymethylcyclopropenes and also allows the oxazolidinones to be recycled (Scheme 3.7).



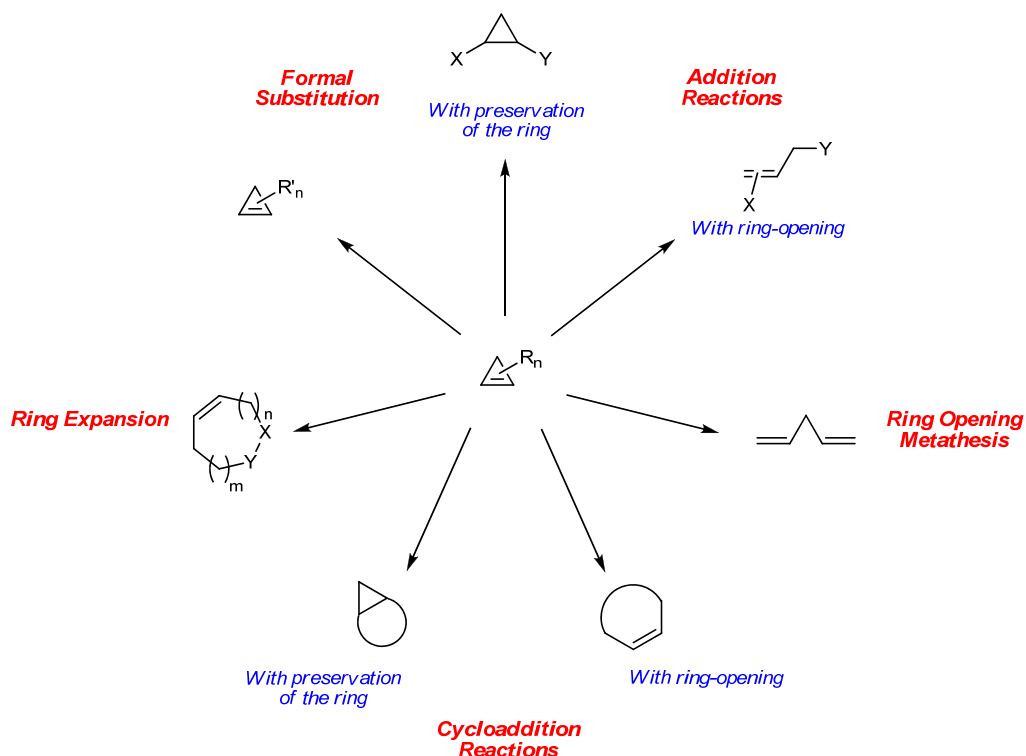
Scheme 3.6 Parallel Kinetic Resolution of Cyclopropenes



Scheme 3.7 Cleavage of the Oxazolidinone with LiBH₄

3.1.2 The General Chemistry of Cyclopropenes

The chemistry of cyclopropenes is extremely diverse and has already been the subject of several excellent reviews by Baird,^{54b} Fox,^{54d} and Gevorgyan.^{54e,f} Some of the main transformations that cyclopropenes undergo are illustrated in Scheme 3.8.

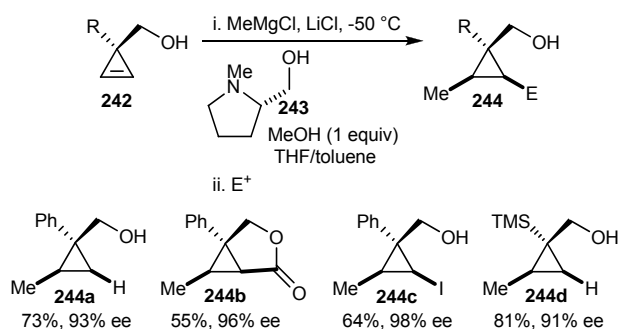


Scheme 3.8 Some of the Main Transformations that Cyclopropenes Undergo

Addition Reactions

The most common type of transformation that cyclopropenes undergo involves transition-metal catalysed addition of various entities across the double bond of the cyclopropene, which can proceed either with or without ring-opening. This reaction type encompasses a diverse range of processes including carbo-⁷² and hydrometallation,⁷³ hydrogenation⁷⁴ and hydroformylation.⁷⁵ For example, Liu and Fox recently reported a highly diastereo- and enantioselective carbomagnesation of cyclopropenylcarbinols using *N*-methylprolinol as a chiral additive and in the presence of methoxide ions.^{72b} Using these conditions, a diverse range of optically

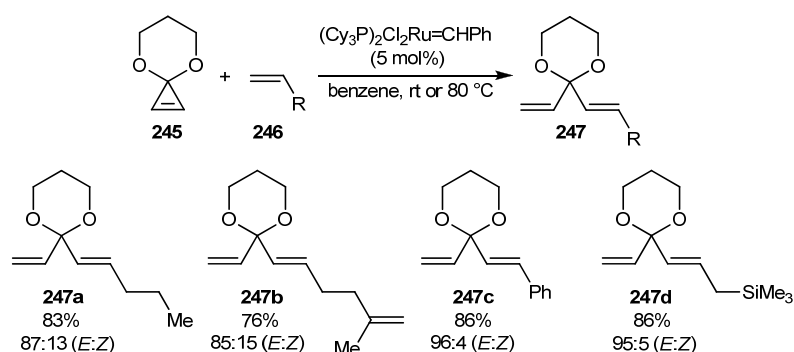
active tri- and tetrasubstituted hydroxymethylcyclopropanes were accessed (Scheme 3.9).



Scheme 3.9 Examples of the Carbomagnesation of Cyclopropenylcarbinols

Ring-Opening Metathesis

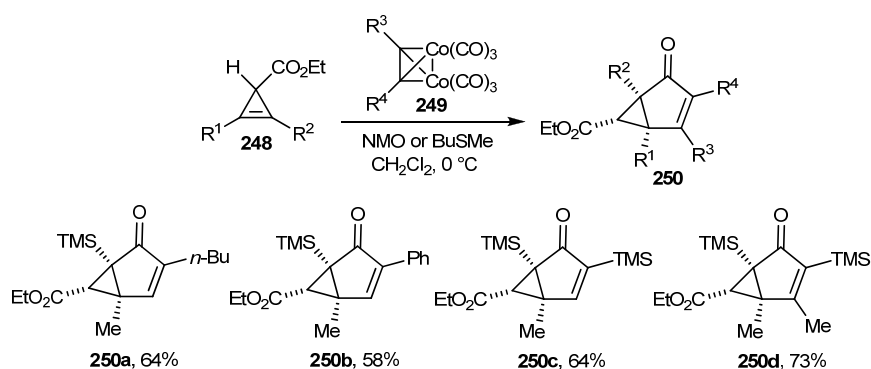
Similar to all cyclic olefins, cyclopropenes can undergo ring-opening metathesis reactions to yield the corresponding acyclic dienes. In 1998, Parrain, Santelli, and co-workers reported an efficient ring-opening cross metathesis of cyclopropenone ketal **245**.⁷⁶ Using the first generation Grubbs catalyst, a variety of terminal olefins underwent ring-opening cross metathesis with **246** to selectively afford protected 1,4-divinyl ketones in moderate to excellent yields (Scheme 3.10).



Scheme 3.10 Examples of the Ring-Opening Cross Metathesis of a Cyclopropenone Ketal

Cycloaddition Reactions

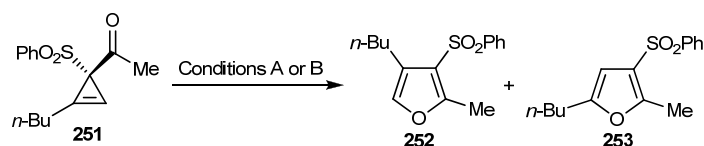
Cyclopropenes have been extensively used in cycloaddition chemistry as these types of reactions allow for the rapid increase in molecular complexity in an atom-economic fashion. For example, Pallerla and Fox have used cyclopropenes in regio- and stereoselective intermolecular Pauson-Khand reactions (Scheme 3.11).⁷⁷ It was demonstrated in these studies that this reaction proceeds readily in the presence of sulfide and *N*-oxide promoters in a highly diastereoselective manner, to afford single diastereoisomers of the corresponding cyclopentenone derivatives.



Scheme 3.11 Examples of the Use of Cyclopropenes in the Pauson-Khand Reaction

Ring Expansion

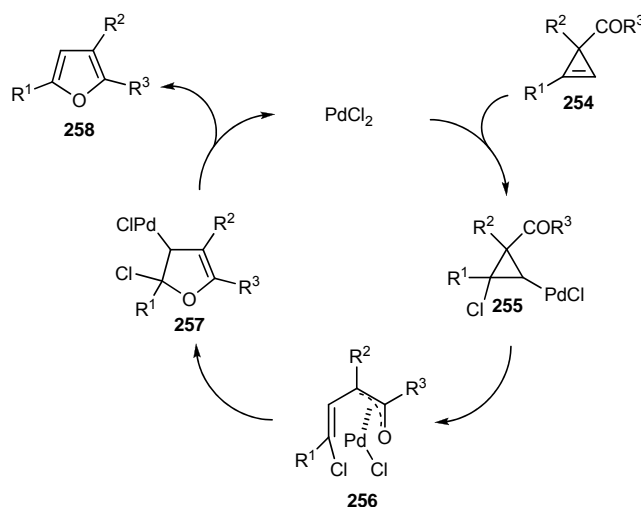
By undergoing ring expansion, cyclopropenes can be used to synthesise a variety of interesting aromatic and heteroaromatic molecules. In 2003, Ma and Zhang reported a highly regioselective ring-opening–cycloisomerisation of cyclopropenylketones to afford either the 2,3,4- or 2,3,5-trisubstituted furans.⁷⁸ It was demonstrated that through exposure of cyclopropenylketone **251** to substoichiometric quantities of CuI in refluxing acetonitrile, 2,3,4-trisubstituted furan **252** could be obtained in excellent yield and regioselectivity (Scheme 3.12). However, by changing catalyst to PdCl₂(CH₃CN)₂ it was possible to completely switch the regioselectivity.



Conditions A: CuI (5 mol%), CH₃CN, reflux 96%, >99:1 (**252**:**253**)
 Conditions B: PdCl₂(CH₃CN)₂ (5 mol%), CHCl₃, reflux 88%, 1:99 (**252**:**253**)

Scheme 3.12 Examples of Ring-Opening Cycloisomerisation

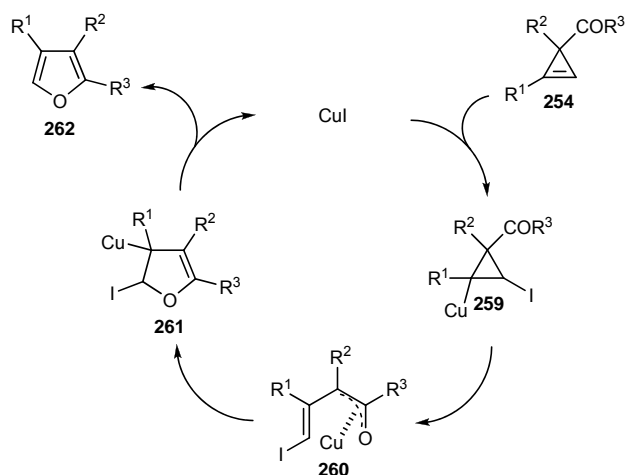
The dramatic difference in the reactivity was explained in terms of the opposite regioselectivity of halometallation in the two different catalytic cycles (Schemes 3.13 and 3.14).⁷⁸ In the presence of catalytic quantities of PdCl₂(CH₃CN)₂, chloropalladation of the C=C bond of the cyclopropenyl ketone **254** would afford the palladium intermediate **255**, in which the palladium atom resides at the least substituted carbon atom (Scheme 3.13). Subsequent β -carbon elimination affords palladium enolate **256**, which in turn undergoes *endo*-oxopalladation, providing dihydrofuran species **257**. Subsequent β -chloride elimination then affords furan **258**.



Scheme 3.13 Possible Mechanism for the Palladium-Catalysed Cycloisomerisation of Cyclopropenyl Ketone **254**

In the copper-catalysed reaction, iodocupration proceeds with the opposite regiochemistry, providing cyclopropyl cuprate **259**, with the metal attached to the

most substituted carbon atom (Scheme 3.14). The final steps are analogous to those shown in Scheme 3.13, involving formation of copper enolate **260** followed by ring closure to give the dihydrofuryl copper species **261**, which ultimately produces furan **262**.



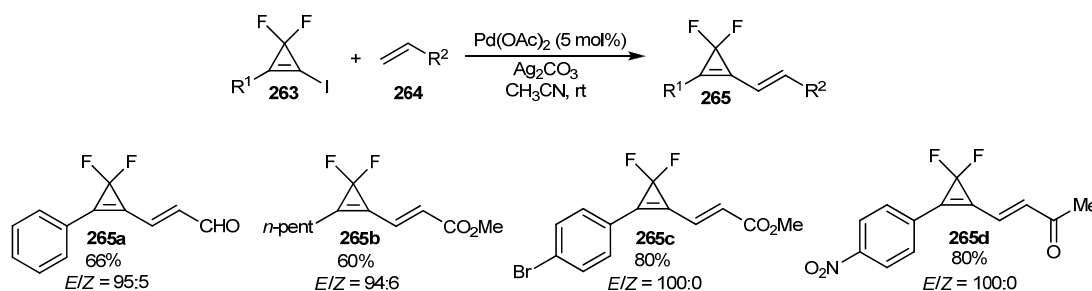
Scheme 3.14 Possible Mechanism for the Copper-Catalysed Cycloisomerisation of Cyclopropenyl Ketone **254**

3.2 Formal Substitution Reactions

Another important type of transformation that cyclopropenes undergo involves formal substitution at the vinylic carbons, which proceed with preservation of the carbocycle skeleton and the strained double bond. In doing so, it is possible to access tetrasubstituted cyclopropenes, which would be difficult to prepare by standard cyclopropanation conditions. Within the Lam group we were interested in developing new, mild, catalytic methodologies for the formal substitution of cyclopropenes as means to access novel tetrasubstituted cyclopropenes. To put our work into context, in this chapter we will review the literature to date on the formal substitution of cyclopropenes.

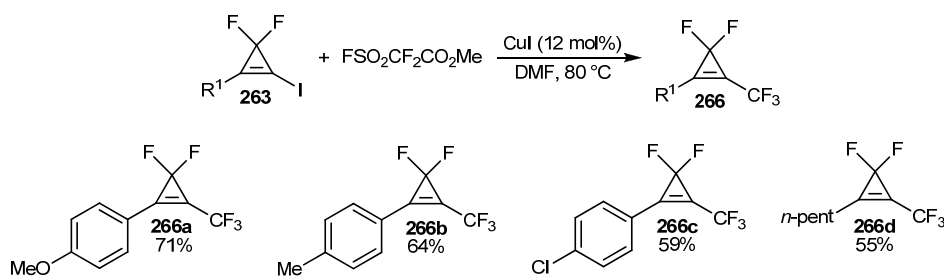
3.2.1 Cyclopropenes as Electrophilic Species

Xu and Chen have demonstrated that 3,3-difluorocyclopropenyl iodides can be used as electrophilic counterparts in the Heck cross-coupling reaction with activated olefins.⁷⁹ Under optimised conditions, a variety of iodocyclopropenes were coupled to α,β -unsaturated carbonyl compounds to yield the corresponding vinylcyclopropenes in moderate to excellent yields and with a high degree of selectivity for the *E*-stereoisomer (Scheme 3.15).



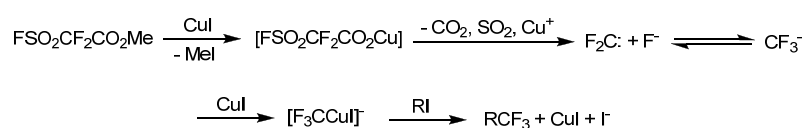
Scheme 3.15 Examples of the Heck Cross-Coupling of Activated Olefins with 3,3-Difluorocyclopropenyl Iodides

Xu and Chen also demonstrated that treatment of iodocyclopropenes **263** with methyl fluorosulfonyldifluoroacetate in the presence of a copper catalyst produced trifluoromethylated cyclopropenes **266** in good yields (Scheme 3.16).⁷⁹



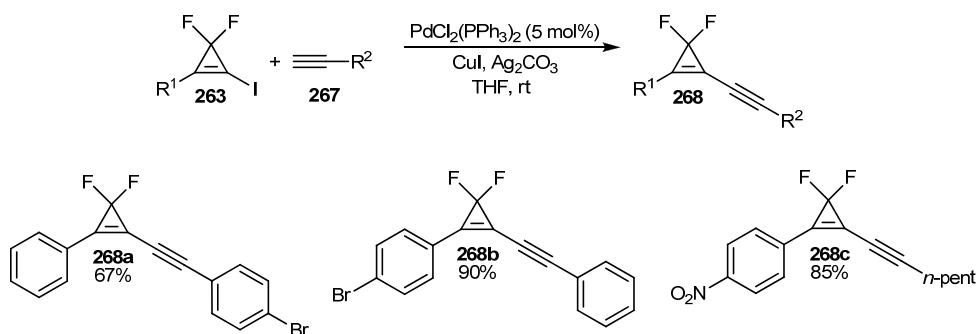
Scheme 3.16 Examples of the Trifluoromethylation of 3,3-Difluorocyclopropenyl Iodides

This trifluoromethylation is believed to involve initial formation of the copper salt of methyl fluorosulfonyldifluoroacetate, with elimination of methyl iodide (Scheme 3.17).⁸⁰ This salt subsequently decarboxylates to yield difluorocarbene and a fluoride ion, which are in equilibrium with trifluoromethide. This equilibrium readily shifts to form trifluoromethide, in the presence of copper iodide, to give $[\text{CF}_3\text{CuI}]^-$. This nucleophilic species then reacts with the iodocyclopropenes to give the desired trifluoromethylated cyclopropenes.



Scheme 3.17 Possible Mechanism for the Trifluoromethylation

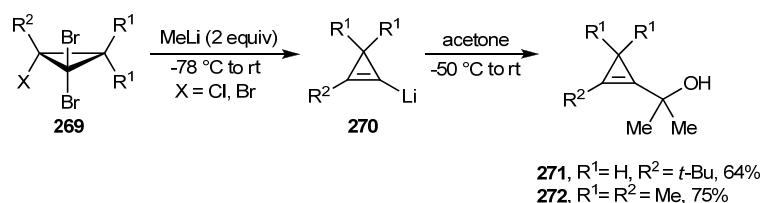
Recently, a new application of 3,3-difluorocyclopropenyl iodides as electrophilic components in Sonogashira cross-coupling reactions was reported by Cheng and Chen.⁸¹ Although this reaction did not proceed under standard conditions for the Sonogashira reaction, by employing stoichiometric silver carbonate as a base, it was possible to access the corresponding 1-alkynylcyclopropenes **268** in moderate to excellent yields (Scheme 3.18).



Scheme 3.18 Examples of the Sonogashira Cross-Coupling of Alkynes with 3,3-Difluorocyclopropenyl Iodides

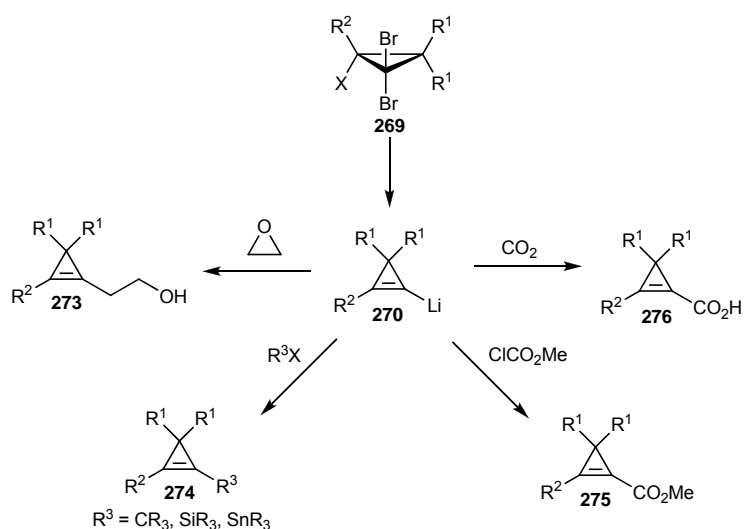
3.2.2 Cyclopropenes as Nucleophilic Species

One of the main methods to functionalise cyclopropenes at the sp^2 -carbon is to generate the cyclopropenylmetal species and then trap with the appropriate electrophile. Cyclopropenylmetal species can be accessed in a number of ways. For example, Baird and co-workers have demonstrated it is possible to synthesise cyclopropenyllithium species (**270**, Scheme 3.19) from 1,1,2-trihalocyclopropanes (halogen = bromine or chlorine).⁵⁶ By trapping this species *in situ* with various electrophiles, a variety of functionalised cyclopropenes have been synthesised. Baird and co-workers have demonstrated that by using acetone as an electrophile it is possible to synthesise cyclopropene derivatives which incorporate an allylic alcohol (Scheme 3.19).^{56b}



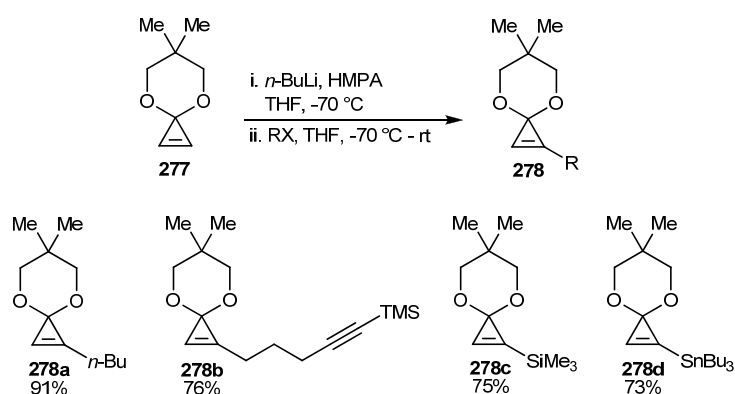
Scheme 3.19 Synthesis and Trapping of Cyclopropenyllithium Species

Other suitable electrophiles include epoxides,⁸² alkyl⁸³ and metal halides,⁸⁴ methyl chloroformate^{56b} and carbon dioxide^{56b} (Scheme 3.20).



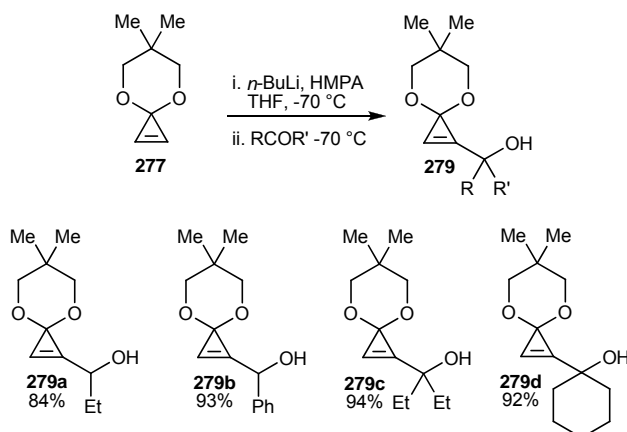
Scheme 3.20 Examples of the Electrophiles used to Trap Cyclopropenyllithium Species

Alternatively, cyclopropenyllithium species can be generated directly by deprotonation of the corresponding cyclopropene using an appropriate alkyl lithium base. Nakamura and co-workers have demonstrated that it is possible to functionalise cyclopropenone ketals using this technique.⁸⁵ Deprotonation with *n*-butyllithium (BuLi), in the presence of HMPA, and subsequent trapping with alkyl and metal halides provided a variety of monosubstituted cyclopropenone ketal derivatives in good to excellent yields (Scheme 3.21).



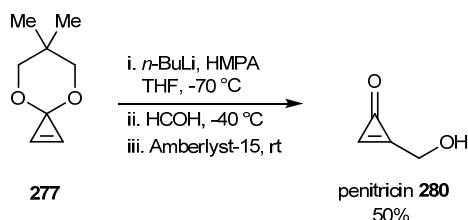
Scheme 3.21 Examples of the Reaction of Cyclopropenyllithium Species with Alkyl and Metal Halides

By using carbonyl compounds as electrophiles in these reactions it was possible to synthesise the corresponding cyclopropenone ketal derivatives, which incorporate allylic alcohol functionality, in good to excellent yields (Scheme 3.22).⁸⁵



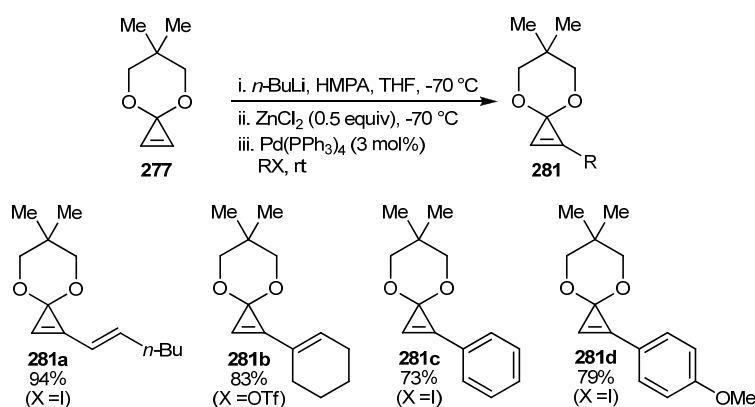
Scheme 3.22 Examples of the Reaction of Cyclopropenyllithium Species with Carbonyl Compounds

Using this technique Nakamura and co-workers have been able to synthesise penitricin **280**, a cyclopropenone derivative, which has been demonstrated to display moderate activity against a broad range of Gram-positive and Gram-negative bacteria.⁸⁵ By trapping the cyclopropenyllithium intermediate that results from reaction of cyclopropenone ketal **277** and *n*-butyllithium, with formaldehyde followed by hydrolysis of the ketal protecting group, it was possible to synthesise penitricin in moderate yield (Scheme 3.23).



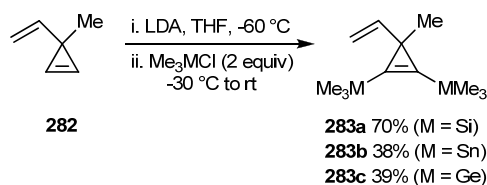
Scheme 3.23 Synthesis of Penitricin **280**

It was further demonstrated that transmetalation of cyclopropenyllithium species with zinc salts, followed by palladium-catalysed cross-coupling with vinyl and aryl iodides or triflates, enabled the synthesis of alkenyl and aryl derivatives (Scheme 3.24).⁸⁵



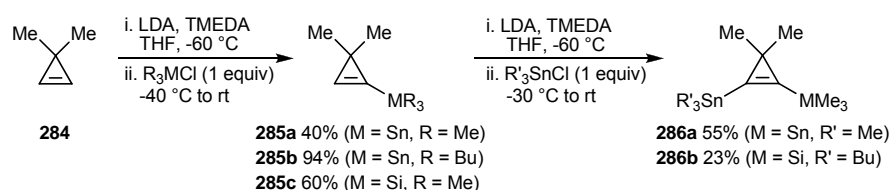
Scheme 3.24 Examples of the Transmetalation and Palladium-Catalysed Cross-Coupling of Cyclopropenyllithium Species

Eckert-Maksić and co-workers have metallated both olefinic carbons in vinylcyclopropene **282** by deprotonation with lithium diisopropylamide (LDA) and trapping with an appropriate metal electrophile (Scheme 3.25).⁸⁶ Using this technique, disilylcyclopropene **283a** was obtained in 70% yield; however, the corresponding tin and germanium analogues were only obtained in moderate yield.



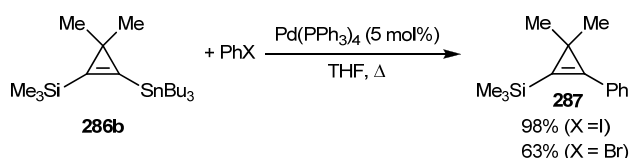
Scheme 3.25 Examples of the Synthesis of Dimetallated Cyclopropenes

De Meijere and co-workers have demonstrated that mono- and dimetallated cyclopropenes can be obtained *via* sequential deprotonation of 3,3-dimethyl-1-cyclopropene **284** with LDA, followed by trapping the corresponding trialkylmetal chloride (Scheme 3.26).⁸⁷ Using this technique, both stannyl- and silylcyclopropene derivatives were obtained in moderate to excellent yields.^{87a} The lower yields obtained for monometallated compounds **285a** and **285c** were attributed to the high volatility of these products. A second deprotonation, followed by trapping with trialkyltin chloride provided *bis*-metallated cyclopropenes **286a** and **286b**.



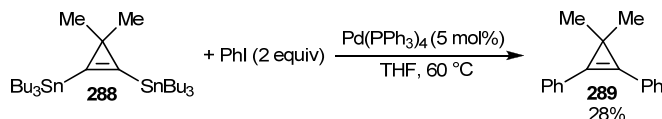
Scheme 3.26 Examples of the Synthesis of Mono- and Dimetallated Cyclopropenes

By coupling cyclopropenylstannane **286b** with phenyl halide, it was possible to obtain the corresponding tetrasubstituted cyclopropene derivative **287** (Scheme 3.27).^{87b} The yields obtained in this Stille cross-coupling were strongly dependent on the electrophilic component, with phenyl iodide and bromide giving 1-phenylcyclopropene **287** in 98% and 63% yield, respectively. However, both phenyl chloride and triflate proved to be very inefficient, and gave the desired cyclopropene in low yield if at all.



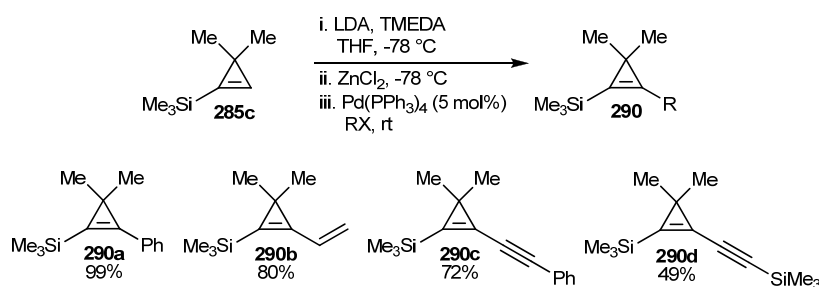
Scheme 3.27 Synthesis of Tetrasubstituted Cyclopropene **287** *via* Stille Cross-Coupling

A double coupling of phenyl iodide with cyclopropenylstannane **288** was partially successful; affording the desired diphenylcyclopropene, **289**, in 28% yield (Scheme 3.28).^{87b}



Scheme 3.28 Synthesis of Diphenylcyclopropene **289** via Stille Cross-Coupling

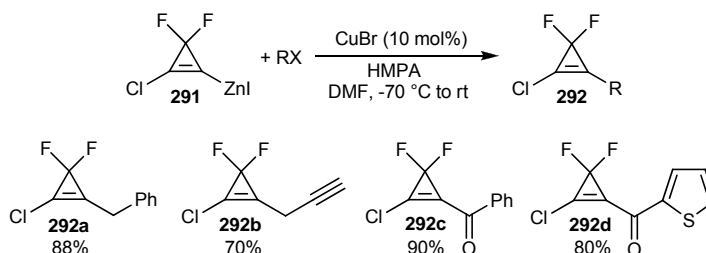
In contrast to cyclopropenylstannanes, the corresponding cyclopropenylzinc derivatives underwent efficient Negishi cross-coupling with alkenyl, alkynyl and aryl derivatives to produce tetrasubstituted cyclopropenes in good to excellent yields (Scheme 3.29).^{87b}



Scheme 3.29 Examples of the Synthesis of Tetrasubstituted Cyclopropenes via Negishi Cross-Coupling

Jeong and co-workers have demonstrated that the 2-chloro-3,3-difluorocyclopropenylzinc reagent **291** can be prepared by treatment of 1-chloro-3,3-difluoro-2-iodocyclopropene with zinc powder.⁸⁸ This reagent has been shown to react with a variety of alkyl and acid halide electrophiles, in the presence of substoichiometric quantities of CuBr, to yield the corresponding functionalised cyclopropenes (Scheme 3.30).⁸⁸ It is believed that the active species in these

reactions is the cyclopropenylcopper species that forms on metathesis of **291** with CuBr, as no reactivity was observed in the absence of the copper catalyst.



Scheme 3.30 Examples of the Copper-Catalysed Functionalisation of Cyclopropenylzinc Reagent **291**

3.3 Conclusions

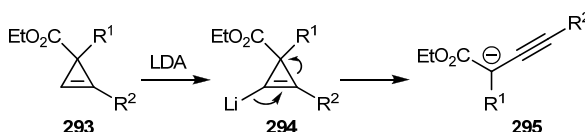
In spite of their relatively simple structure, cyclopropenes have attracted the interest of many research groups for over 100 years. Much of this attention has been due to the unique structure that cyclopropene and its derivatives possess, with their highly strained nature allowing them to undergo reactions that are not thermodynamically feasible for other olefins. Hence, cyclopropenes have been shown to undergo a broad range of reactions, ranging from hydrometallation to cycloisomerisation. One type of reaction that has interested us has been formal substitution at the vinylic carbons and in this chapter we have demonstrated that this can be achieved in a variety of different ways. We have illustrated that cyclopropenyl iodides can be used as the electrophilic component in a variety of palladium-catalysed cross coupling reactions. Conversely we have seen that by synthesising cyclopropenylmetal species, whether this be from the corresponding 1,1,2-trihalogencyclopropane or by direct metallation, cyclopropenes can be considered as the nucleophilic component in such transformations. However, using either technique it is possible to gain access to a diverse range of tri- and tetrasubstituted cyclopropenes.

4. Development of Novel Methodologies for the Silylation and Stannylation of Base-Sensitive Cyclopropenes⁸⁹

4.1 Introduction

Formal substitution at the vinylic carbons of cyclopropenes is a useful way to access tri- and tetrasubstituted cyclopropenes. In the previous chapter we illustrated that one of the main ways to functionalise cyclopropenes is by direct metallation with lithium reagents. The resulting cyclopropenyl lithium species can be directly trapped with an electrophile or transmetalated with zinc(II) chloride and then cross-coupled with an appropriate aryl, heteroaryl, alkenyl or alkynyl halide.

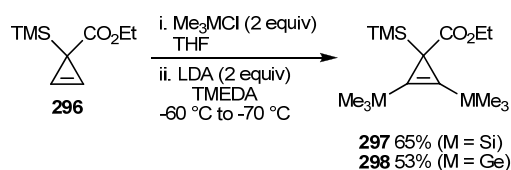
While direct metallation with lithium reagents has proven to be a very useful method for the functionalisation of the cyclopropene double bond, this approach often fails with substrates bearing base-sensitive functionalities. For example, attempts at the direct metallation of ester-substituted cyclopropene **293** result in rapid ring-opening *via* the stabilised propargyl intermediate **295**, leading to mixtures of allenyl and alkynyl derivatives (Scheme 4.1).⁹⁰



Scheme 4.1 Ring-Opening of Ester Substituted Cyclopropene **293**

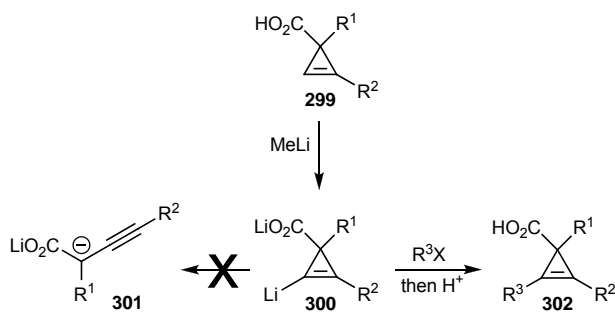
To circumvent ring cleavage, Eckert-Maksić developed an inverse addition procedure, in which the electrophile is added prior to the addition of the base

(Scheme 4.2).^{90b,c} However, this method is limited to very reactive silyl and germyl electrophiles only.



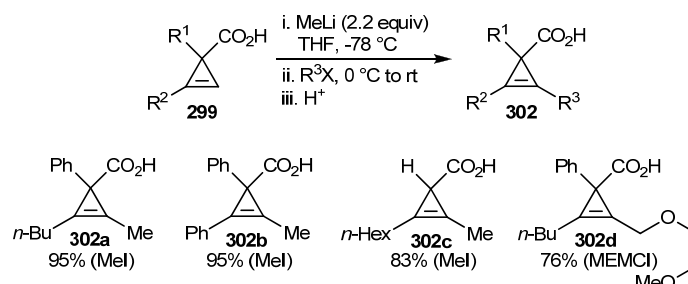
Scheme 4.2 Inverse Addition Protocol

A more elegant solution to this problem has been developed by Fox and co-workers, who demonstrated that carboxylic acid derivatives can be used instead of esters in a one-pot deprotonation/electrophile trapping reaction.⁹¹ Fox reasoned that dilithiated species **300** (Scheme 4.3), which forms on exposure of the carboxylic acid derivatives to base, is more stable than the corresponding monolithiated species (**294**, Scheme 4.1) because of the increase in Coulombic repulsion that would occur on ring-opening. It was also assumed that the more reactive carbanion would react in preference to the carboxylate to selectively produce cyclopropene **302**.



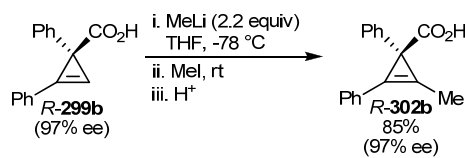
Scheme 4.3 Dianion Strategy for Forming Internal Cyclopropenes

These assumptions proved to be correct, as exposure of different terminal cyclopropene carboxylic acids to 2.2 equivalents of methyl lithium (MeLi), followed by trapping with various electrophiles afforded the corresponding internal cyclopropenes in good to excellent yields (Scheme 4.4).⁹¹



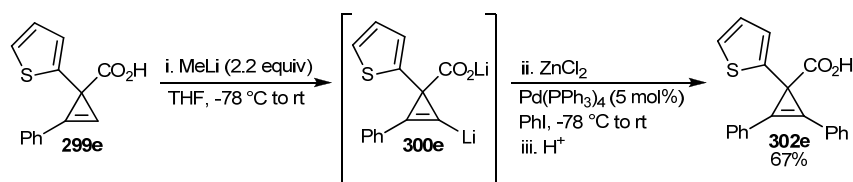
Scheme 4.4 Cyclopropene Dianion Alkylation

This metallation/alkylation sequence was shown to be stereospecific as exposure of (*R*)-1,3-diphenylcyclopropene carboxylic acid **R-299b** to standard conditions yielded the corresponding internal cyclopropene **R-302b** with no loss of enantiomeric excess (Scheme 4.5).⁹¹



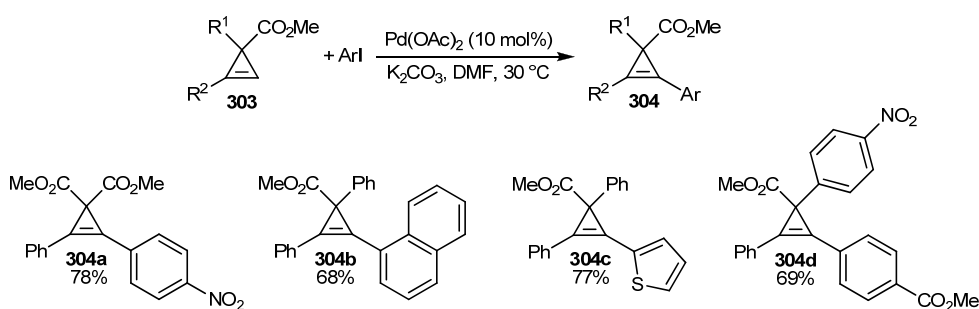
Scheme 4.5 Dianion Formation/Alkylation Occurs Without Loss of Stereochemical Integrity

Fox and co-workers also demonstrated that the cyclopropene carboxylate dianions formed using this methodology can serve as nucleophiles in palladium-catalysed cross-coupling chemistry.⁹¹ Transmetalation of dianion **300e** with ZnCl₂, followed by the addition of catalytic Pd(PPh₃)₄ and phenyl iodide leads to formation of diphenylcyclopropene **302e** in good yield (Scheme 4.6).



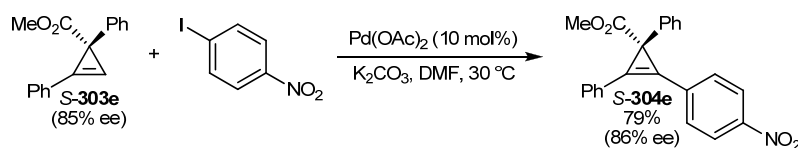
Scheme 4.6 Dianion Formation/Palladium-Catalysed Arylation

A Heck-type arylation of cyclopropenes, proceeding with preservation of the three-membered ring, has recently been reported by Gevorgyan and co-workers.⁹² This method allows for the direct introduction of an aryl-substituent, under very mild conditions, to base-sensitive ester-substituted cyclopropenes. Under optimised conditions, a variety of aryl and heteroaryl iodides were coupled to afford the corresponding tetrasubstituted cyclopropenes in good yield (Scheme 4.7).



Scheme 4.7 Palladium-Catalysed Arylation of Cyclopropenes

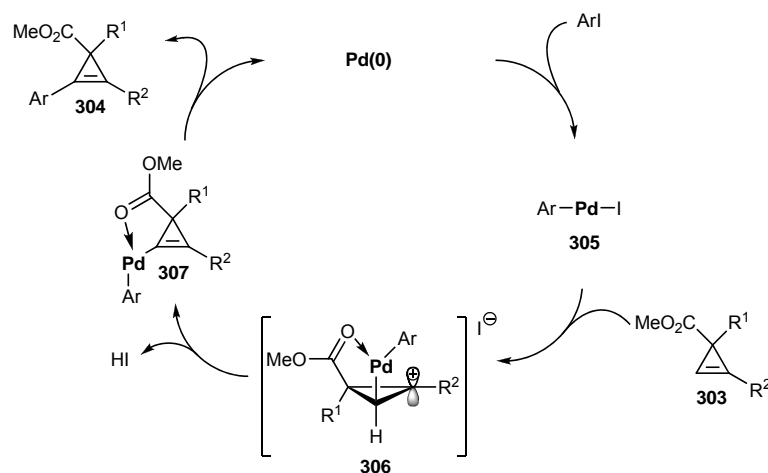
Application of this methodology to non-racemic substrates provided direct access to optically active tetrasubstituted cyclopropenes, which are unavailable *via* asymmetric cyclopropenation methods (Scheme 4.8).^{66,67,69}



Scheme 4.8 Application of Heck-Type Arylation Methodology to Non-Racemic Substrates

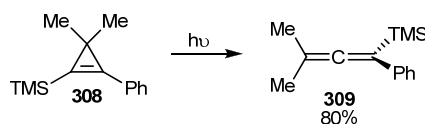
Mechanistic studies conducted on this Heck-type arylation appear to suggest that it proceeds through cyclopropyl cation intermediate **306**, formed by nucleophilic attack on ArPdI (formed after oxidative addition of Pd(0) to ArI) by cyclopropene **303**

(Scheme 4.9).⁹² Subsequent proton loss and reductive elimination then yields the desired arylated cyclopropene.



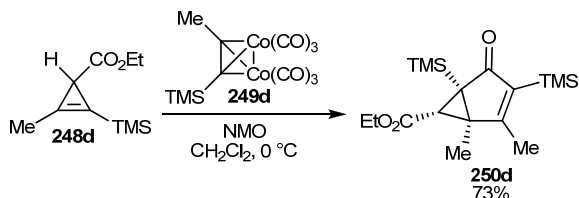
Scheme 4.9 Proposed Mechanism for the Palladium-Catalysed Arylation of Cyclopropenes

While the work of both Fox and Gevorgyan has greatly expanded the scope of the formal substitutions of cyclopropenes, we were keen to develop new routes to metallated cyclopropenes, particularly those which incorporate a silyl or trialkylstannyl substituent. We believed that the latter could potentially serve as useful precursors to a range of novel cyclopropenes through Stille cross-coupling reactions.^{93,94} Furthermore, cyclopropenes that contain a silyl substituent on the alkene have already been demonstrated to be important synthetic intermediates in the synthesis of allenylsilanes (Scheme 4.10).⁹⁵



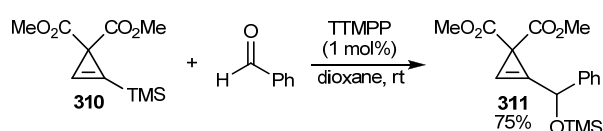
Scheme 4.10 Photochemical Rearrangement of Silylated Cyclopropene **308**

In addition to this, the trimethylsilyl group has been demonstrated to efficiently control the regioselectivity of transformations such as the Pauson-Khand reaction (Scheme 4.11).⁷⁷



Scheme 4.11 Example of Regioselective Pauson-Khand Reaction

More recently, Gevorgyan and co-workers have recently described the use of 1-silylcyclopropenes in sila-Morita-Baylis-Hillman reactions (Scheme 4.12).⁹⁶



Scheme 4.12 Example of the use of 1-Silylcyclopropene **310** in the Sila-Morita-Baylis-Hillman Reaction

This chapter illustrates our efforts towards the development of new and mild protocols for the silylation and stannylation of cyclopropenes, which incorporate base-sensitive functionality. In addition, we will illustrate the utility of the resulting products in an iron-catalysed carbometallation ring-opening methodology developed with the group and, where applicable, in the Stille cross-coupling. In doing so we will demonstrate that silyl- and stannylcyclopropenes serve as useful precursors to a variety of novel and interesting molecules.

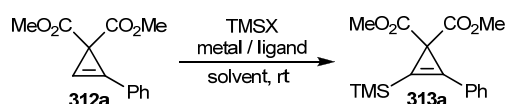
4.2 Results and Discussion

4.2.1 Direct Silylation of Cyclopropenes

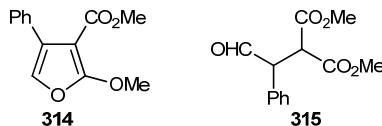
Cyclopropenes often possess “alkyne-like” reactivity because of the strong s-character of the olefinic C-H bond.⁹⁷ On this basis, we decided to examine reaction conditions that have been successfully applied to the metallation of terminal alkynes, and in particular those that use weak bases in combination with soft Lewis acids, such as copper,⁹⁸ zinc⁹⁹ and silver salts.¹⁰⁰ In addition, we hoped to simplify the experimental procedure by using silylating reagents containing a functional group that also functions as the base to effect deprotonation of the cyclopropene, instead of the more conventional silyl chloride or triflates (where an additional stoichiometric base is required).

Our initial experiments began with cyclopropene **312a** (Table 4.1), which upon attempted silylation using LDA and TMSCl afforded a complex mixture of products. Using commercially available *N,N*-dimethyltrimethylsilylamine as the silylating agent¹⁰¹ and 5 mol% of CuI in toluene at room temperature, none of the desired product **313a** was observed (entry 1). Instead, complete conversion into furan **314** took place, which has precedent in the work of Ma and Zhang.⁷⁸ The use of Cu(acac)₂, AgOAc, or Zn(OTf)₂ led only to varying quantities of furan **314** and aldehyde **315**¹⁰² in low to moderate conversions (entries 2-4). Changing the silylating agent to (trifluoromethyl)trimethylsilane¹⁰³ also afforded no product using Cu(acac)₂ (entry 5). However, we were pleased to observe that the combination of 5 mol% of Cu(acac)₂ and dppe¹⁰⁴ provided the desired product **313a** in an encouraging 40% yield (entry 6), the remainder of material being unreacted **312a**. Switching the solvent to THF increased the yield of **313a** to 88% (entry 7). A control experiment performed in the absence of Cu(acac)₂ demonstrated that both copper and dppe are required for the reaction to occur (entry 8).

Table 4.1 Identification of Optimum Reaction Conditions for Silylation of Cyclopropene **312a**^a



Side-products observed:



Entry	Metal / ligand (5 mol % of each)	TMSX (2 equiv)	Solvent	Yield of 313a (%) ^b
1	CuI	TMSNMe ₂	toluene	0 ^c
2	Cu(acac) ₂	TMSNMe ₂	toluene	0 ^d
3	AgOAc	TMSNMe ₂	toluene	0 ^e
4	Zn(OTf) ₂	TMSNMe ₂	toluene	0 ^e
5	Cu(acac) ₂	TMSCF ₃	toluene	0 (SM)
6	Cu(acac) ₂ / dppe	TMSCF ₃	toluene	40
7	Cu(acac) ₂ / dppe	TMSCF ₃	THF	88
8	dppe	TMSCF ₃	THF	0 (SM)

^a Reactions were conducted using 0.20 mmol of **312a** in 0.7 mL of solvent. ^b Isolated yield. ^c Complete conversion into furan **314** was observed. ^d *Ca.* 72% of **314** and 8% of **315** was observed. ^e *Ca.* 20% of **315** was observed. dppe = 1,2-bis(diphenylphosphino)ethane. SM = starting material.

Having established satisfactory reaction conditions with cyclopropene **312a**, we proceeded to explore the scope of the direct silylation process with a range of other 1,3,3-trisubstituted cyclopropenes (Table 4.2). Analogues of **312a**, containing other aromatic or alkyl substituents on the alkene, successfully underwent silylation to provide silylcyclopropenes **313b-312e** in 69-99% yield (entries 1-4). Replacement of one of the methyl esters at the 3-position with an aryl substituent, or both of the methyl esters with ethyl esters was also tolerated, leading to silylcyclopropenes **313f-313j** in 66-84% yield (entries 5-9). The efficiencies of these reactions are not markedly affected upon increasing the scale. For example, cyclopropene **313d** was formed in 99% and 93% yields on 0.20 and 2.00 mmol scales, respectively (entry 3).

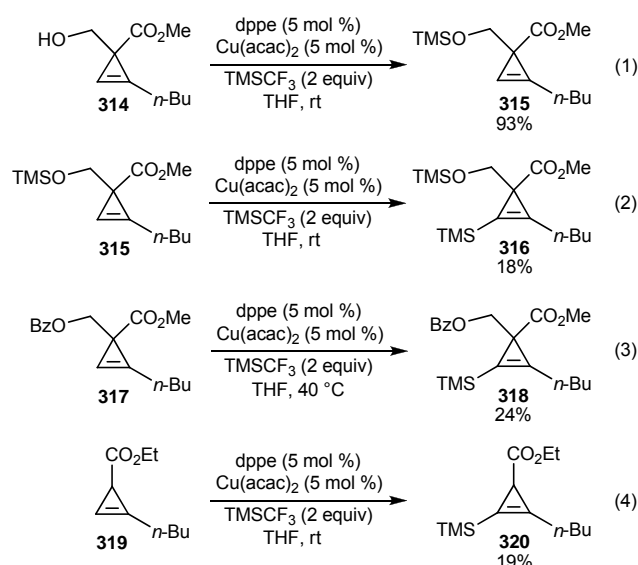
Table 4.2 Direct Silylation of Assorted Cyclopropenes^a

$\text{312b, 312d-312k} + \text{TMSCF}_3 \xrightarrow[\text{THF, rt}]{\text{dppe (5 mol \%), Cu(acac)}_2 \text{ (5 mol \%)}} \text{313b-313j}$

entry	substrate	product	yield (%) ^b
1	312b R = 4-MePh		313b 90
2	 312d R = 1-naphthyl		313c 76
3	 312e R = <i>n</i> -Bu		313d 99 (93) ^c
4	312f R = CH ₂ CH ₂ OBz		313e 69
5	 312g		313f 83
6	 312h R = Ph		313g 66
7	 312i R = <i>n</i> -Bu		313h 68
8	 312j		313i 84
9	 312k		313j 80

^a Unless otherwise stated, reactions were conducted using 0.20 mmol of cyclopropene, 0.01 mmol of Cu(acac)₂ and 0.01 mmol of dppe in THF (0.7 mL). ^b Cited yields are of isolated material. ^c Yield in parentheses refers to a reaction conducted using 2.0 mmol of **312e**, 0.10 mmol of Cu(acac)₂ and 0.10 mmol of dppe in THF (7 mL).

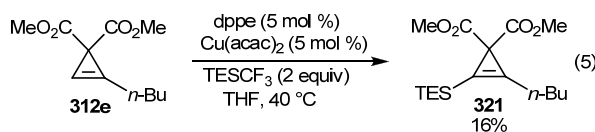
Further variation of the substituents at the 3-position gave cyclopropenes, which proved to be less competent substrates for silylation (Scheme 4.13). Perhaps unsurprisingly, cyclopropene **314**, containing a free hydroxyl group, underwent *O*-silylation in preference to *C*-silylation (eq 1). However, resubjection of **315** to the reaction conditions provided silylcyclopropene **316** in only 18% yield (eq 2). The lower efficiency with which 3-alkyl-substituted cyclopropenes are silylated seems to be a general phenomenon, as evidenced by the reaction of cyclopropene **317** at 40 °C (eq 3).¹⁰⁵ 3-Monosubstituted cyclopropene **319** was also found to be less reactive, providing **320** in 19% yield (eq 4). Whether cyclopropenes **315**, **317** and **319** possess higher pK_a values compared with cyclopropenes **312a-312k**, and whether this presumed difference in acidity is responsible for their attenuated reactivity remains to be confirmed.¹⁰⁶



Scheme 4.13 Effect of Substitution at the 3-Position of the Cyclopropene on the Efficiency of Direct Silylation

The use of (trifluoromethyl)triethylsilane as the silylating agent led to the formation of triethylsilylcyclopropene **321** in only 16% yield from **312e** at 40 °C (eq 5). We

attribute this poor yield (compare with **313d** in Table 4.2) to increased steric hindrance provided by the bulkier reagent.



To gain some insight into these reactions, the silylation of deuterated cyclopropene **322** (eq 6) was followed by ^{19}F NMR spectroscopy (Fig. 4.1). As the reaction proceeded, a new signal appeared at -80 ppm (t, $J_{\text{FD}} = 12.1$ Hz), showing that DCF_3 was formed. Since substrate **322** was the only source of deuterium in the system, this observation suggests that at some stage, a trifluoromethide species abstracted a deuteron from the substrate.

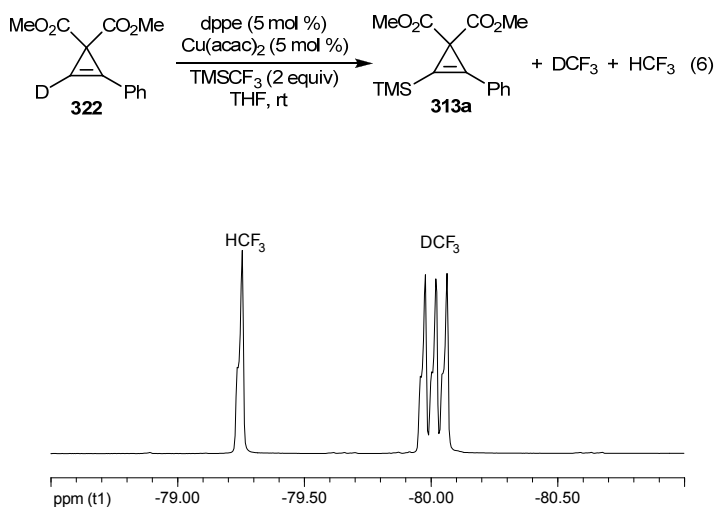
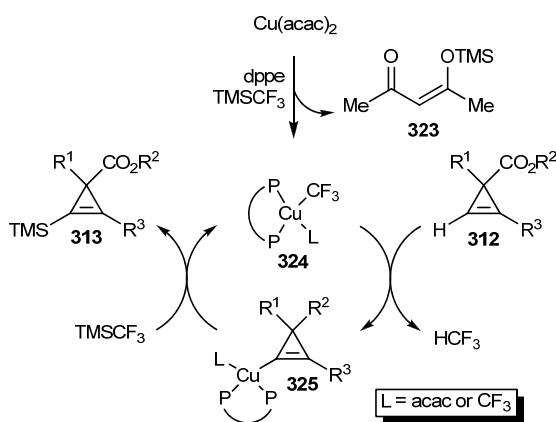


Fig. 4.1 ^{19}F NMR Spectrum of the Silylation of Deuterated Cyclopropene **322** (eq 6)

The production of DCF_3 was also accompanied by the formation of HCF_3 (eq 6), which most likely resulted from reaction of the trifluoromethide species with trace moisture present in the mixture. EPR and cyclic voltammetry experiments suggest that copper largely retains the +2 oxidation state in these reactions, though we cannot

exclude the possibility that the active catalytic species is a Cu(I) complex that exists as a minor component. Based on this information, we have speculated on a possible mechanism for the direct silylation of cyclopropenes (Scheme 4.14). Treatment of a solution of Cu(acac)₂ and dppe with TMSCF₃ might lead to the complex **324**, containing one or two Cu–CF₃ bonds.¹⁰⁷ Reaction of substrate **312** with **324** would generate fluoroform along with cyclopropenylcopper species **325**, which in turn could react with TMSCF₃ to give the silylcyclopropene, **313**, and regenerate **324**. However, alternative mechanisms involving electrophilic silylation¹⁰¹ or hypervalent silicon intermediates^{103a} cannot be excluded.

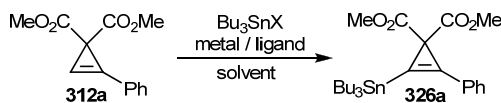


Scheme 4.14 Possible Mechanism for the Direct Silylation of Cyclopropenes

4.2.2 Direct Stannylation of Cyclopropenes

Having developed conditions for the direct silylation of base-sensitive cyclopropenes, we hoped that by replacing TMSCF₃ with Bu₃SnCF₃ we would be able to access the corresponding stannylated cyclopropenes. Unfortunately, exposure of cyclopropene **312a** to 5 mol% Cu(acac)₂ and dppe in the presence of Bu₃SnCF₃ resulted in low conversion to the desired product **326a** (entry 1, Table 4.3).

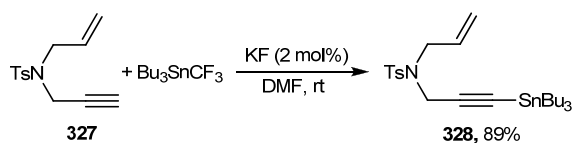
Table 4.3. Identification of Optimum Reaction Conditions for Stannylation of Cyclopropene **312a**^a



entry	metal salt / ligand (equiv of each)	Bu ₃ SnX (2 equiv)	solvent	temp (°C)	convn (%) ^b
1	Cu(acac) ₂ / dppe (0.05)	Bu ₃ SnCF ₃	THF	rt	10
2	Cu(acac) ₂ / dppe (0.05)	Bu ₃ SnCF ₂ CF ₃	THF	rt	25
3	KF (1.0)	Bu ₃ SnCF ₃	DMF	rt	54
4	KF (1.0)	Bu ₃ SnCF ₃	DMF	40	67
5	KF (1.0)	Bu ₃ SnCF ₂ CF ₃	DMF	rt	84
6	KF (1.0)	Bu ₃ SnCF ₂ CF ₃	DMF	40	98 ^c

^a Reactions were conducted using 0.20 mmol of **312a** in 0.8 mL of solvent. ^b Determined by ¹H NMR analysis of the unpurified reaction mixtures. ^c For isolated yield see entry 1, Table 4.4.

Efforts to increase the conversion through variation of the copper source were also unproductive. However, it was noticed that use of Bu₃SnCF₂CF₃ improved the conversion slightly (entry 2).¹⁰⁸ Upon examining related reactions in the literature, we encountered a single example of a direct stannylation of an alkyne using Bu₃SnCF₃ and catalytic KF (Scheme 4.15).^{103a}



Scheme 4.15 Direct Stannylation of an Alkyne using Bu₃SnCF₃ and KF

Since cyclopropenes often exhibit properties that are more similar in nature to alkynes rather than alkenes⁹⁷ this procedure was deemed to possess potential merit, and we therefore applied these conditions to the stannylation of **312a**. Although the use of catalytic KF was not suitable, stoichiometric KF provided a promising 54%

conversion to **326a** using Bu_3SnCF_3 in DMF (entry 3). Further increases in conversion were realised by raising the temperature (entry 4, and compare entries 5 and 6) and through the use of $\text{Bu}_3\text{SnCF}_2\text{CF}_3$ (compare entries 3 and 4 with entries 5 and 6, respectively).¹⁰⁸ The optimum conditions employed $\text{Bu}_3\text{SnCF}_2\text{CF}_3$ and stoichiometric KF in DMF at 40 °C (entry 6).

The generality of this procedure was investigated using a variety of base-sensitive 1,3,3-trisubstituted cyclopropenes (Table 4.4). Analogues of **312a** containing other aromatic or alkyl substituents on the alkene successfully underwent stannylation to provide stannylcyclopropenes **326b–326d** in 56–87% yield (entries 2-4). In addition to methyl esters, other tolerated functional groups at C3 included ethyl esters and either electron-rich or electron-deficient aromatics, resulting in stannylcyclopropenes **326e–326h** in 63–88% yield (entries 5-8).

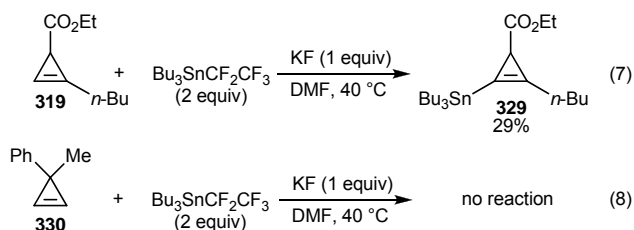
Table 4.4 Direct Stannylation of Various Cyclopropenes^a

$$\text{Cyclopropene (312a-k)} + \text{Bu}_3\text{SnCF}_2\text{CF}_3 \xrightarrow[\text{DMF, 40 } ^\circ\text{C}]{\text{KF (1 equiv)}} \text{Stannylated Cyclopropene (326a-h)}$$

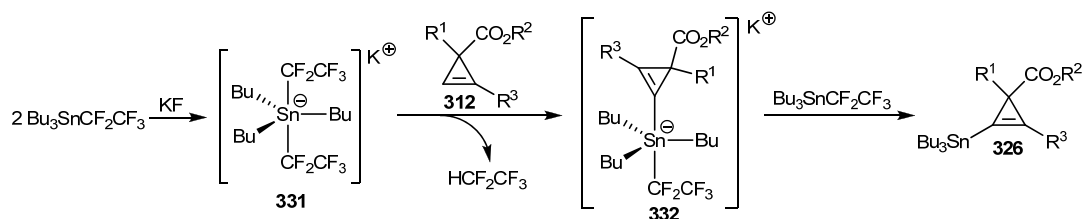
Entry	substrate	product	yield (%) ^b
1	312a R = Ph		326a 82
2	 312c R = 4-BrPh		326b 63
3	 312d R = 1-naphthyl		326c 56
4	312e R = <i>n</i> -Bu		326d 87
5	 312g		326e 69
6	 312h		326f 65
7	 312j		326g 63
8	 312k		326h 88

^a Reactions were conducted using 0.20 mmol of cyclopropene, 0.20 mmol of KF, and 0.40 mmol of Bu₃SnCF₂CF₃. ^b Cited yields are of isolated material.

Two activating substituents (esters or aromatics) at C3 of the cyclopropene are required for stannylation to proceed efficiently.¹⁰⁶ For example, cyclopropene **319** provided alkenylstannane **329** in only 29% yield (eq 7), while no reaction was observed with **330** (eq 8).



A possible mechanism for this interesting stannylation reaction is presented in Scheme 4.16. Here, the combination of KF and $\text{Bu}_3\text{SnCF}_2\text{CF}_3$ results in formation of pentacoordinated stannate **331**.¹⁰⁹ This hypervalent tin reagent then abstracts the olefinic proton from cyclopropene **312** to yield stannate **332**, which then reacts with further $\text{Bu}_3\text{SnCF}_2\text{CF}_3$ to furnish the desired stannylcyclopropene **326**. However, with no evidence for this mechanism, alternative pathways cannot be ruled out.

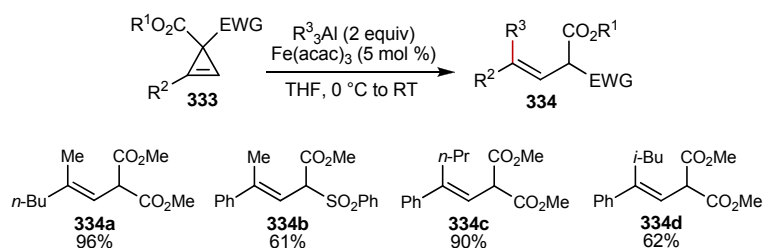


Scheme 4.16 Proposed Mechanism for the Direct Stannylation of Cyclopropenes

4.2.3 Applications of Silyl- and Stannylcyclopropenes

Having developed mild protocols for the direct silylation and stannylation of base-sensitive cyclopropenes, the utility of the resulting products was investigated. Within the Lam group we have developed an iron-catalysed cyclopropene carbometallation ring-opening sequence, which enables the efficient synthesis of tri- and

tetrasubstituted alkenes.¹¹⁰ Under optimised conditions it was demonstrated that a variety of trisubstituted cyclopropenes reacted smoothly with trialkylaluminum reagents to provide the corresponding trisubstituted alkenes in good to excellent yields and with high regioselectivities (Scheme 4.17; results obtained by Yi Wang).



Scheme 4.17 Iron-Catalysed Carbometallation Ring-Opening of Cyclopropenes with Trialkylaluminum reagents

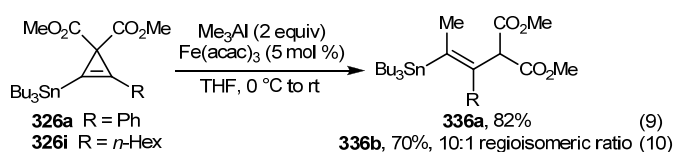
Having developed conditions for carbometallation ring-opening of trisubstituted cyclopropenes it was decided to apply these conditions to the more challenging tetrasubstituted cyclopropenes. Under conditions identical to those employed previously, 1-trimethylsilylcyclopropenes **313a**, **313b** and **313d** underwent smooth reaction to provide the corresponding α,β,β' -trisubstituted vinylsilanes **335a-335e** (Table 4.5; results obtained by Yi Wang). Importantly, the sense of regioselectivity obtained in these reactions is opposite to that obtained for the trisubstituted cyclopropenes, with the alkyl group delivered preferentially to the TMS-bearing carbon. Regioselectivity was highest (>19:1) with aryl-substituted cyclopropenes (preparation of **313a-313d**). With alkyl-substituted cyclopropenes, formation of the opposite regioisomer was detected (preparation **335e**).

Table 4.5. α,β,β' -Trisubstituted Vinylsilanes Synthesis^a

entry	substrate	R^2_3Al	product	Yield (%) ^b
1	 313a	Me_3Al	 335a $R^1 = Me$	89
2	 313b	Et_3Al	 335b $R^1 = Et$	73
3	 313c	Me_3Al	 335c $R^1 = Me$	71
4	 313d	$n-Pr_3Al$	 335d $R^1 = n-Pr$	88
5	 313e	Me_3Al	 335e $R^1 = Me$	68 ^c

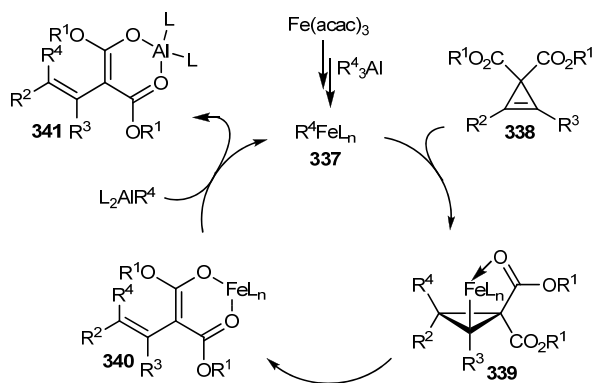
^a Reactions were conducted using 0.20 mmol of substrate in THF (2 mL). ^b Cited yields are of isolated material. ^c Obtained as a 6:1 ratio of regioisomers.

In similar fashion, the use of 1-stannylcyclopropenes enabled the synthesis of α,β,β' -trisubstituted vinylstannanes (eq 9 and eq 10).



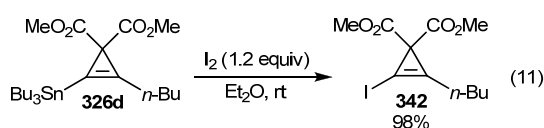
Scheme 4.18 illustrates a possible catalytic cycle for these reactions. Reaction of $Fe(acac)_3$ with the trialkylaluminum most likely generates a low-valent iron species **337**. *Syn*-carbometallation of substrate **338** with **337** would generate cyclopropyl iron species **339**. β -Carbon elimination¹¹¹ of **339** with conservation of the *cis*-relationship between R^2 and R^3 would then provide iron enolate **340**, which can undergo

transmetallation with trialkylaluminum species to provide aluminum enolate **341** and regenerate **337**. The assisted β -carbon elimination of **339** by Lewis acid coordination of the trialkylaluminum to the malonate to provide enolate **341** directly is a possibility that should also be considered.



Scheme 4.18 Possible Catalytic Cycle for the Iron-Catalysed Carbometallation Ring-Opening of Cyclopropenes

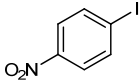
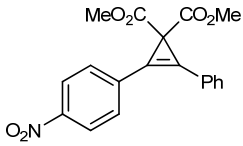
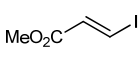
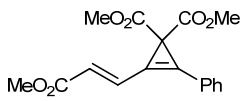
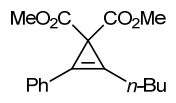
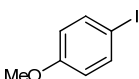
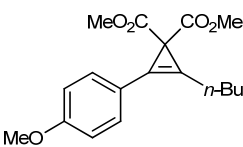

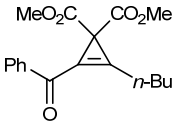
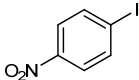
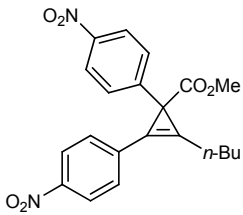

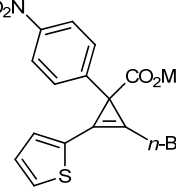
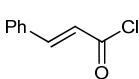
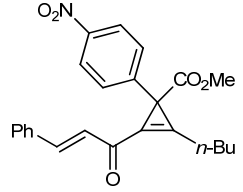
In addition to serving as precursors for α,β,β -trisubstituted vinylstannanes, 1-stannylcyclopropenes also undergo facile tin-halogen exchange to yield the corresponding iodocyclopropenes. For example, treatment of stannylcyclopropene **326d** with I_2 in Et_2O resulted in formation of iodocyclopropene **342** in near-quantitative yield (eq 11).¹¹²



Our principal goal for the synthesis of stannylcyclopropenes was to establish the utility of these interesting building blocks in the synthesis of other tetrasubstituted cyclopropenes, through the use Stille coupling reactions.⁹⁴ The only prior examples of these types of reactions were reported by Untiedt and de Meijere, using a limited

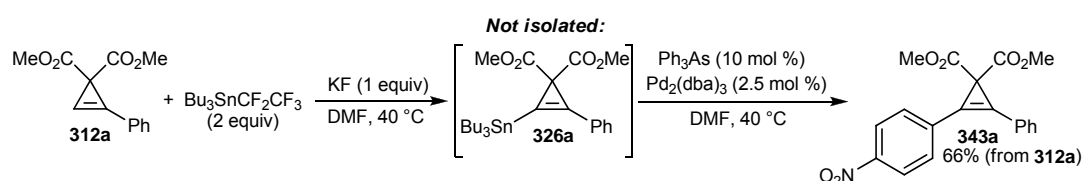
selection of coupling partners (Scheme 3.27 and 3.28, Chapter 3), and it was therefore of interest to ascertain whether more highly functionalised cyclopropenes could be prepared using stannylcyclopropenes **326** and a wider selection of electrophiles. Fortunately, using a combination of $\text{Pd}_2(\text{dba})_3$ and Ph_3As ¹¹³ as the precatalyst components, stannylcyclopropenes **326a**, **326d**, and **326h** smoothly underwent crossing-coupling with a range of organic halides (Table 4.6). Aromatic (entries 1, 3, 4, and 6) and heteroaromatic (entry 7) iodides were found to be effective electrophiles, and as expected, the more reactive electron-deficient iodoarenes resulted in higher yields (compare entries 1 and 6 with entries 3, 4, and 7).¹¹⁴ The use of an alkenyl iodide provided diene **343b** (entry 2) in 87% yield. Notably, acid chlorides were also competent electrophiles, providing cyclopropenes **343e** and **343h**, which would be difficult to prepare using existing methods (entries 5 and 8).⁵⁴

Table 4.6 Stille Coupling Reaction of Stannylcyclopropenes^a

$ \begin{array}{c} \text{R}^1 \quad \text{CO}_2\text{R}^2 \\ \diagup \quad \diagdown \\ \text{C} \\ \diagdown \quad \diagup \\ \text{Bu}_3\text{Sn} \quad \text{R}^3 \\ \textbf{326a, d or h} \end{array} + \text{R}^4\text{-X} \xrightarrow[\text{THF}]{\text{Ph}_3\text{As (10 mol \%)} \quad \text{Pd}_2(\text{dba})_3 \text{ (2.5 mol \%)}} \begin{array}{c} \text{R}^1 \quad \text{CO}_2\text{R}^2 \\ \diagup \quad \diagdown \\ \text{C} \\ \diagdown \quad \diagup \\ \text{R}^4 \quad \text{R}^3 \\ \textbf{343a-343h} \end{array} $					
entry	stannane	R ⁴ -X	temp (°C)	product	yield (%) ^b
1	326a		40		343a 91
2			40		343b 87
3	326d	PhI	55		343c 72
4			55		343d 56
5			40		343e 78
6	326h		40		343f 99
7			60		343g 61
8 ^c			40		343h 69

^a Unless otherwise stated, reactions were conducted using 0.10 mmol of stannylcyclopropene and 0.11 mmol of organic halide. ^b Isolated yield. ^c Reaction conducted using 1.5 equivalents of cinnamoyl chloride.

In certain cases, we have found that stannylcyclopropenes **326** sometimes undergo protodestannylation during long-term storage. In light of this observation, a one-pot direct stannylation/Stille cross-coupling reaction, which removes the necessity to isolate the stannylcyclopropene intermediate, was developed (Scheme 4.19). Upon completion of the stannylation of cyclopropene **312a** as observed by TLC analysis, a solution of 1-iodo-4-nitrobenzene (1.1 equivalent), $\text{Pd}_2(\text{dba})_3$ (2.5 mol%), and Ph_3As (10 mol%) in DMF was added, and heating was continued at 40 °C to eventually provide cyclopropene **343a** in 66% overall yield.



Scheme 4.19 One-Pot Direct Stannylation/Stille Coupling

4.3 Conclusions

In conclusion, we have developed two new mild and operationally simple methods for the direct metallation of cyclopropenes, containing base-sensitive functionality. By employing TMSCF_3 in conjunction with substoichiometric quantities of $\text{Cu}(\text{acac})_2$ and dppe, a variety of 1,3,3-trisubstituted cyclopropenes underwent silylation to provide the corresponding silylated cyclopropenes in good to excellent yields. Unfortunately, attempts to broaden the scope of this methodology to 3-alkyl-substituted cyclopropenes proved unsuccessful. Although mechanistic studies into this interesting silylation methodology suggest deprotonation of the cyclopropene by a trifluoromethide species, we can only really speculate on the actual mechanism of this reaction.

A mild method for the direct stannylation of cyclopropenes, employing $\text{Bu}_3\text{SnCF}_2\text{CF}_3$ and KF has also been developed. Using this methodology we have been able to synthesise novel 1-stannylcyclopropenes in good to excellent yield. However, in a similar fashion to the direct silylation methodology that we have developed, two activating substituents (esters or aromatics) at C3 of the cyclopropene are required for stannylation to proceed efficiently.

We have also demonstrated that both the silyl- and stannylcyclopropenes accessed using these two methodologies serve as useful precursors to a variety of interesting molecules. By using an iron-catalysed carbometallation ring-opening methodology developed within the group, we can gain access to a variety of interesting trisubstituted vinylsilanes and vinylstannanes. We have also shown that stannylcyclopropenes can be used as the nucleophilic component in Stille cross-couplings and thereby give rise to a variety of new and exciting tetrasubstituted cyclopropenes.

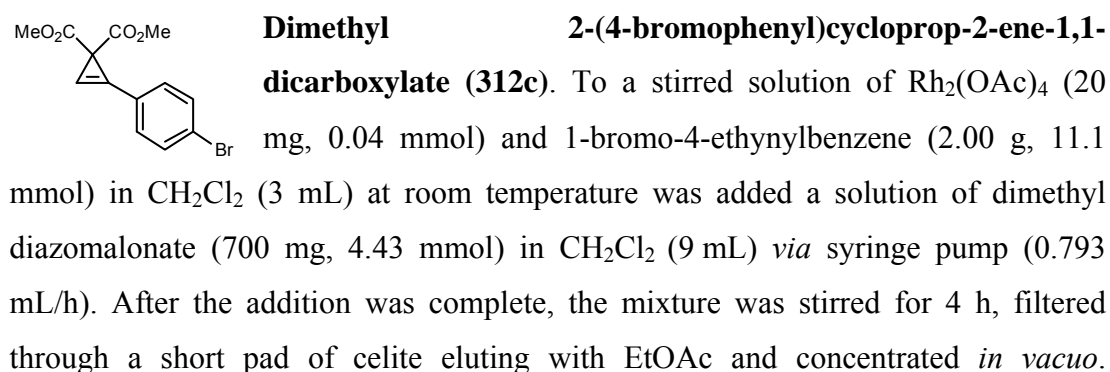
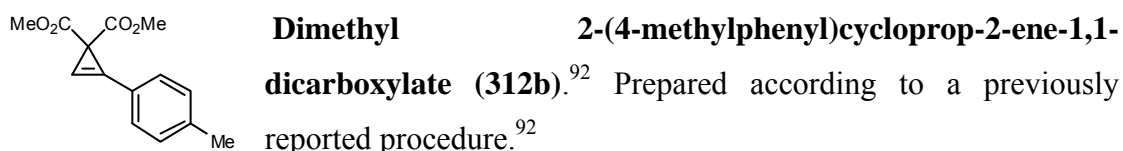
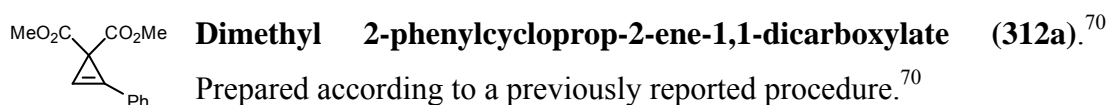
4.4 Experimental

General Information

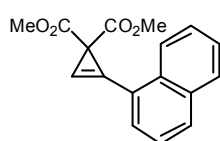
All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. CH₂Cl₂, THF and toluene were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontour.com. All other commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilen 60F₂₅₄ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.¹¹⁵ Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in CHCl₃. ¹H NMR spectra were recorded on a Bruker DPX360 (360 MHz) spectrometer or a Bruker ARX250 (250 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard (CDCl₃ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ¹³C NMR spectra were recorded on a Bruker DPX360 (90.6 MHz) spectrometer or a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard (CDCl₃ at 77.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. Proton-decoupled ¹⁹F NMR spectra were recorded on a Bruker spectrometer at F. Hoffmann-La Roche, Basel (282 MHz). High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer or a Finnigan MAT 95XP spectrometer, using either the electrospray (ES) positive ion mode or the electron impact (EI) mode at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea. Stated calculated mass values refer to that of the *ion* (i.e. the actual species being detected),

not that of the neutral parent compound. X-band EPR data were recorded on an X-band Bruker ER 200-D SRC spectrometer connected to a datalink 486DX desktop PC running EPR acquisition system version 2.42. 0.01M Solutions in THF were run in a quartz flat cell. The copper hyperfine coupling constants (A^{Cu}) and the spectroscopic splitting factor (g) were measured using the program WinEPR SimFonia Version 1.25,¹¹⁶ which was also used to simulate spectra. Electrochemical studies were carried out using a DELL GX110 PC with General Purpose Electrochemical System (GPES), version 4.8 software, connected to an autolab system containing a μ Autolab type III potentiostat. The technique used a three electrode configuration, with a 0.5 mm diameter Pt disc working electrode, a Pt rod counter electrode and an Ag/AgCl (saturated KCl) reference electrode against which the ferrocenium/ferrocene coupling was measured to be +0.55 V. The supporting electrolyte was 0.1 M tetrabutylammonium tetrafluoroborate (TBABF₄) in THF.

Preparation of Cyclopropenes

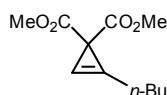


Purification of the residue by column chromatography (heptane→30% EtOAc/heptane) gave the *cyclopropene* **312c** (702 mg, 51%) as a pale yellow oil. IR (film) 2951, 1720 (C=O), 1599, 1518, 1346, 1209, 1107, 1026, 852, 706 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.60 (2H, dm, J = 8.5 Hz, ArH), 7.50 (2H, dm, J = 8.5 Hz, ArH), 6.95 (1H, s, =CH), 3.75 (6H, s, 2 x OCH₃); ^{13}C NMR (62.9 MHz, CDCl_3) δ 170.8 (2 x C), 132.2 (2 x CH), 131.6 (2 x CH), 125.1 (C), 122.9 (C), 111.5 (C), 96.2 (CH), 52.4 (2 x CH₃), 32.8 (C); HRMS (ES) Exact mass calcd for $\text{C}_{13}\text{H}_{12}\text{O}_4\text{Br}$ $[\text{M}+\text{H}]^+$: 310.9913, found: 310.9907.

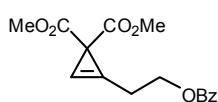


Dimethyl 2-(naphthalen-1-yl)cycloprop-2-ene-1,1-dicarboxylate (312d). To a stirred mixture of $\text{Rh}_2(\text{OAc})_4$ (9.8 mg, 0.022 mmol) and 1-naphthylacetylene (847 mg, 5.56 mmol) at

room temperature was added a solution of dimethyl diazomalonate (352 mg, 2.22 mmol) in CH_2Cl_2 (10 mL) *via* syringe pump (0.793 mL/h). After the addition was complete, the mixture was stirred for 16 h, filtered through a short pad of celite eluting with CH_2Cl_2 and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) gave the *cyclopropene* **312d** as a pale yellow solid (338 mg, 54%). m.p. 106-108 °C; IR (CHCl_3) 3140, 2951, 1732 (C=O), 1589, 1508, 1222, 1064, 986, 804, 775 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 8.37-8.35 (1H, m, ArH), 7.97-7.91 (2H, m, ArH), 7.77-7.75 (1H, m, ArH), 7.68-7.53 (3H, m, ArH), 7.23 (1H, s, =CH), 3.76 (6H, s, 2 x CH₃); ^{13}C NMR (62.9 MHz, CDCl_3) δ 171.1 (2 x C), 133.4 (C), 132.1 (C), 131.4 (CH), 130.8 (CH), 128.6 (CH), 127.5 (CH), 126.6 (CH), 125.4 (CH), 124.3 (CH), 120.3 (C), 110.6 (C), 97.3 (CH), 52.4 (2 x CH₃), 31.4 (C); HRMS (ES) Exact mass calcd for $\text{C}_{17}\text{H}_{15}\text{O}_4$ $[\text{M}+\text{H}]^+$: 283.0965, found: 283.0968.

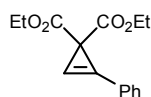


Dimethyl 2-butylcycloprop-2-ene-1,1-dicarboxylate (312e).¹¹⁷
Prepared according to a previously reported procedure.¹¹⁷



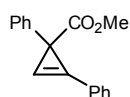
Dimethyl 2-(2-benzoyloxyethyl)cycloprop-2-ene-1,1-dicarboxylate (312f).

To a stirred mixture of $\text{Rh}_2(\text{OAc})_4$ (17.3 mg, 0.04 mmol) and but-3-ynyl benzoate¹¹⁸ (6.00 g, 34.5 mmol) in CH_2Cl_2 (2 mL) at room temperature was added a solution of dimethyl diazomalonate (1.03 g, 6.50 mmol) in CH_2Cl_2 (8 mL) *via* syringe pump (0.793 mL/h). After the addition was complete, the mixture was stirred for 16 h, filtered through a short pad of celite eluting with CH_2Cl_2 and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→30% EtOAc/hexane) gave the *cyclopropene* **312f** as a yellow oil (1.49 g, 75%). IR (film) 3137, 2953, 1715 (C=O), 1601, 1435, 1382, 1276, 1116, 1069, 713 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 8.03-8.00 (2H, m, ArH), 7.58-7.54 (1H, m, ArH), 7.46-7.41 (2H, m, ArH), 6.56 (1H, s, =CH), 4.55 (2H, t, $J = 9.7$ Hz, CH_2O), 3.66 (6H, s, 2 x CH_3), 3.06 (2H, t, $J = 9.7$ Hz, $\text{CH}_2\text{CH}_2\text{O}$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 171.4 (2 x C), 166.2 (C), 133.1 (CH), 129.7 (2 x CH), 129.6 (2 x CH), 128.3 (2 x CH), 111.4 (C), 96.0 (CH), 61.2 (CH_2), 52.2 (2 x CH_3), 32.2 (C), 24.0 (CH_2); HRMS (ES) Exact mass calcd for $\text{C}_{16}\text{H}_{17}\text{O}_6$ $[\text{M}+\text{H}]^+$: 305.1020, found: 305.1019.

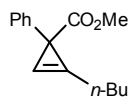


Diethyl 2-phenylcycloprop-2-ene-1,1-dicarboxylate (312g).¹¹⁹

Prepared according to a previously reported procedure.¹¹⁹

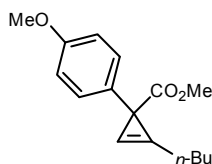


Methyl 1,2-diphenylcycloprop-2-enecarboxylate (312h).⁷⁰ Prepared according to a previously reported procedure.⁷⁰



Methyl 2-butyl-1-phenylcycloprop-2-enecarboxylate (312i).⁷⁰

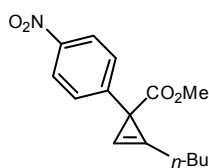
Prepared according to a previously reported procedure.⁷⁰



Methyl 2-butyl-1-(4-methoxyphenyl)cycloprop-2-enecarboxylate (312j).

To a stirred mixture of $\text{Rh}_2(\text{OAc})_4$ (43.0 mg, 0.10 mmol) and 1-hexyne (2.09 g, 25.5 mmol) at room temperature was added a solution of methyl *p*-methoxyphenyldiazoacetate¹²⁰ (1.00 g,

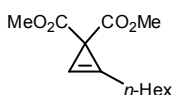
4.85 mmol) in CH₂Cl₂ (9 mL) *via* syringe pump (0.793 mL/h). After the addition was complete, the mixture was stirred for 2 h, filtered through a short pad of celite eluting with EtOAc and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→10% EtOAc/hexane) gave the *cyclopropene* **312j** as a yellow oil (727 mg, 58%). IR (film) 2955, 1718 (C=O), 1610, 1512, 1465, 1247, 1219, 1175, 1029, 838 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.22-7.18 (2H, m, ArH), 6.86-6.82 (2H, m, ArH), 6.66 (1H, t, *J* = 1.4 Hz, =CH), 3.80 (3H, s, OCH₃), 3.69 (3H, s, OCH₃), 2.58-2.54 (2H, td, *J* = 7.4, 1.4 Hz, =CCH₂), 1.64-1.54 (2H, m, CH₂), 1.42-1.31 (2H, m, CH₂), 0.90 (3H, t, *J* = 7.3 Hz, CH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 176.2 (C), 158.0 (C), 134.0 (C), 129.3 (2 x CH), 121.3 (C), 113.4 (2 x CH), 97.0 (CH), 55.2 (CH₃), 51.9 (CH₃), 32.3 (C), 28.8 (CH₂), 24.1 (CH₂), 22.2 (CH₂), 13.7 (CH₃); HRMS (ES) Exact mass calcd for C₁₆H₂₄NO₄ [M+NH₄]⁺: 278.1751, found: 278.1754.



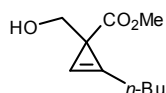
Methyl 2-butyl-1-(4-nitrophenyl)cycloprop-2-enecarboxylate

(312k). To a stirred mixture of Rh₂(OAc)₄ (10.0 mg, 0.02 mmol) and 1-hexyne (483 mg, 5.88 mmol) at room temperature was added a solution of methyl *p*-nitrophenyldiazoacetate¹²⁰ (500 mg,

2.26 mmol) in CH₂Cl₂ (9 mL) *via* syringe pump (0.793 mL/h). After the addition was complete, the mixture was stirred for 5 h, filtered through a short pad of celite eluting with EtOAc and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→30% EtOAc/hexane) gave the *cyclopropene* **312k** as a yellow oil (397 mg, 64%). IR (film) 2956, 1718 (C=O), 1597, 1517, 1348, 1287, 1211, 1031, 852, 708 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.16-8.12 (2H, m, ArH), 7.48-7.44 (2H, m, ArH), 6.66 (1H, t, *J* = 1.4 Hz, =CH), 3.71 (3H, s, OCH₃), 2.55 (2H, td, *J* = 7.5, 1.4 Hz, =CCH₂), 1.59-1.51 (2H, m, CH₂), 1.40-1.30 (2H, m, CH₂), 0.88 (3H, t, *J* = 7.3 Hz, CH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 174.4 (C), 149.5 (C), 146.2 (C), 129.0 (2 x CH), 123.1 (2 x CH), 120.1 (C), 95.8 (CH), 52.1 (CH₃), 32.9 (C), 28.6 (CH₂), 23.9 (CH₂), 22.1 (CH₂), 13.5 (CH₃); LRMS (ES) Mass calcd for C₁₅H₁₈NO₄ [M+H]⁺: 276.1, found: 276.1.

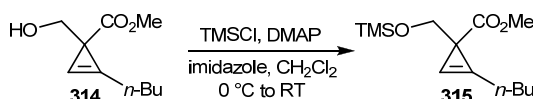


Dimethyl 2-hexylcycloprop-2-ene-1,1-dicarboxylate (312I). To a stirred solution of $\text{Rh}_2(\text{OAc})_4$ (44 mg, 0.10 mmol) and 1-octyne (2.20 g, 20.0 mmol) in CH_2Cl_2 (2 mL) at room temperature was added a solution of dimethyl diazomalonate (1.58 g, 10.0 mmol) in CH_2Cl_2 (8 mL) *via* syringe pump (0.793 mL/h). After the addition was complete, the mixture was stirred for 8 h, filtered through a short pad of celite eluting with CH_2Cl_2 , and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane \rightarrow 10% EtOAc/hexane) gave the *cyclopropene* **312I** as a yellow oil (1.26 g, 52%). IR (film) 3139, 2955, 2860, 1734 ($\text{C}=\text{O}$), 1436, 1279, 1111, 1065, 841 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 6.34 (1H, s, $=\text{CH}$), 3.69 (6H, s, 2 x OCH_3), 2.52 (2H, t, $J = 7.1$ Hz, $=\text{CCH}_2$), 1.60-1.54 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.36-1.24 (6H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.86 (3H, t, $J = 6.8$ Hz, CH_2CH_3); ^{13}C NMR (62.9 MHz, CDCl_3) δ 171.8 (2 x C), 114.5 (C), 93.4 (CH), 52.1 (2 x CH_3), 31.3 (CH_2), 28.6 (CH_2), 26.3 (CH_2), 23.9 (CH_2), 22.4 (CH_2), 13.9 (CH_3); HRMS (ES) Exact mass calcd for $\text{C}_{13}\text{H}_{21}\text{O}_4$ $[\text{M}+\text{H}]^+$: 241.1434, found: 241.1432.



Methyl 2-butyl-1-hydroxymethylcycloprop-2-ene-1-carboxylate (314).⁷⁰ Prepared according to a previously reported procedure.⁷⁰

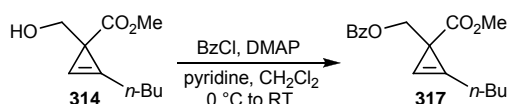
Methyl 2-butyl-1-trimethylsilyloxymethylcycloprop-2-ene-1-carboxylate (315)



To a stirred solution of the cyclopropene **314** (300 mg, 1.63 mmol), imidazole (278 mg, 4.08 mmol) and DMAP (7.6 mg, 0.06 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added TMSCl (250 μL , 1.95 mmol) dropwise over 1 min. The reaction mixture was stirred at room temperature for 19 h and then H_2O (20 mL) was added. The aqueous layer was separated and extracted with Et_2O (3 x 20 mL) and the combined organic layers were washed with 1 M HCl solution (20 mL), saturated aqueous NaHCO_3 solution (20 mL), and brine (20 mL). The combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. Purification of the residue by column

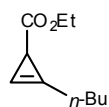
chromatography (hexane→10% EtOAc/hexane) afforded the *silyl ether* **315** (225 mg, 54%) as a colourless oil. IR (film) 2957, 1718 (C=O), 1458, 1435, 1250, 1111, 1065, 876, 842, 749 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 6.37 (1H, s, =CH), 3.95 (1H, d, J = 10.8 Hz, OCH₂), 3.80 (1H, d, J = 10.8 Hz, OCH₂), 3.63 (3H, s, OCH₃), 2.46 (2H, td, J = 7.3, 1.4 Hz, =CCH₂), 1.59-1.51 (2H, m, CH₂), 1.43-1.33 (2H, m, CH₂), 0.91 (3H, t, J = 7.3 Hz, CH₂CH₃), 0.07 (9H, s, Si(CH₃)₃); ^{13}C NMR (62.9 MHz, CDCl_3) δ 176.2 (C), 118.5 (C), 96.5 (CH), 64.5 (CH₂), 51.5 (CH₃), 31.1 (C), 29.0 (CH₂), 24.4 (CH₂), 22.2 (CH₂), 13.7 (CH₃), -0.5 (3 x CH₃); HRMS (ES) Exact mass calcd for $\text{C}_{13}\text{H}_{25}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$: 257.1567, found: 257.1568.

Methyl 1-benzoyloxymethyl-2-butylcycloprop-2-ene-1-carboxylate (**317**)

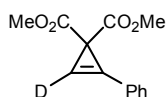


To a stirred solution of the cyclopropene **314** (143 mg, 0.78 mmol), pyridine (190 μL , 2.34 mmol) and DMAP (4.8 mg, 0.04 mmol) in CH_2Cl_2 (7 mL) at 0 °C was added benzoyl chloride (100 μL , 0.86 mmol) dropwise over 1 min. The reaction mixture was stirred at room temperature for 1.5 h and then concentrated *in vacuo*. The resulting residue was dissolved in EtOAc (20 mL) and washed with saturated aqueous NH_4Cl solution (20 mL), saturated aqueous NaHCO_3 solution (20 mL), brine (20 mL) and H_2O (20 mL). The organic layer was dried (MgSO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→30% EtOAc/hexane) afforded the *benzoyl ester* **317** (172 mg, 76%) as a colourless oil. IR (film) 2956, 1716 (C=O), 1451, 1377, 1274, 1176, 1110, 1069, 1026, 714 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 8.05-8.01 (2H, m, ArH), 7.59-7.52 (1H, m, ArH), 7.47-7.40 (2H, m, ArH), 6.45 (1H, t, J = 1.4 Hz, =CH), 4.66 (1H, d, J = 11.5 Hz, OCH₂), 4.60 (1H, d, J = 11.5 Hz, OCH₂), 3.69 (3H, s, OCH₃), 2.52 (2H, td, J = 7.3, 1.4 Hz, =CCH₂), 1.63-1.51 (2H, m, CH₂), 1.46-1.31 (2H, m, CH₂), 0.89 (3H, t, J = 7.3 Hz, CH₂CH₃); ^{13}C NMR (62.9 MHz, CDCl_3) δ 175.3 (C), 166.4 (C), 132.8 (CH), 130.4 (C), 129.5 (2 x CH), 128.3 (2 x CH), 118.2 (C), 96.6 (CH), 68.0

(CH₂), 51.9 (CH₃), 28.9 (CH₂), 28.4 (C), 24.3 (CH₂), 22.2 (CH₂), 13.6 (CH₃); HRMS (ES) Exact mass calcd for C₁₇H₂₁O₄ [M+H]⁺: 289.1434, found: 289.1437.



Ethyl-2-butylcycloprop-2-enecarboxylate (319).¹²¹ Prepared according to a previously reported procedure.¹²¹

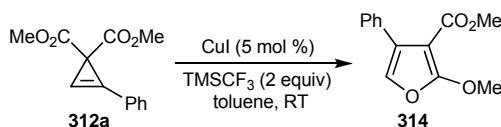


Dimethyl 2-phenylcycloprop-2-ene-1,1-dicarboxylate-*d*₁ (322).⁹² Prepared according to a previously reported procedure.⁹²



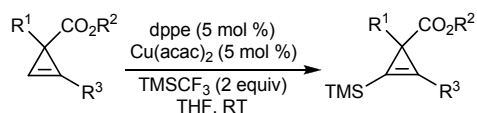
3-Methyl-3-phenylcyclopropene (330).⁷³ Prepared according to a previously reported procedure.⁷³

Synthesis of methyl 2-methoxy-4-phenyl-3-furancarboxylate (**314**)



A solution of cyclopropene **312a** (46mg, 0.20 mmol) and CuI (2 mg, 0.01 mmol) in toluene (0.7 mL) was stirred at room temperature for 30 min. TMSNMe₂ (63 μL, 0.40 mmol) was then added in one portion and the reaction was stirred at room temperature for 18 h. The reaction mixture was filtered through a short plug of SiO₂ (*ca.* 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→25% EtOAc/hexane) afforded the *furan* **314** (43 mg, 92%) as a pale yellow oil. IR (film) 2951, 1712 (C=O), 1599, 1469, 1406, 1296, 1130, 1086, 993, 698 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.42-7.32 (5H, m, ArH), 6.91 (1H, s, =CH), 4.14 (3H, s, OCH₃), 3.72 (3H, s, OCH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 163.5 (C), 163.1 (C), 131.7 (C), 129.6 (CH), 129.0 (2 x CH), 128.2 (C), 127.8 (2 x CH), 127.5 (CH), 105.7 (C), 57.8 (CH₃), 50.9 (CH₃).

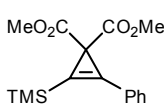
Copper-Catalyzed Silylation of Cyclopropenes: General Procedure A



A solution of the appropriate cyclopropene (0.20 mmol), Cu(acac)₂ (2.6 mg, 0.01 mmol) and dppe (4.0 mg, 0.01 mmol) in THF (0.7 mL) was stirred at room temperature for 30 min. TMSCF₃ (59 µL, 0.40 mmol) was then added in one portion and the reaction was stirred at room temperature until complete consumption of the cyclopropene as observed by TLC analysis, or until no further reaction progress could be seen. The reaction mixture was filtered through a short plug of SiO₂ (*ca.* 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/hexane) afforded the silylated product.

General Procedure B

This was identical to General Procedure A except that the reaction was heated at 40 °C.

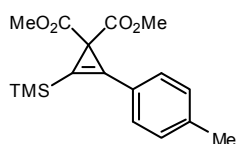


Dimethyl

2-phenyl-3-trimethylsilylcycloprop-2-ene-1,1-

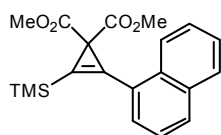
dicarboxylate (313a).

The title compound was prepared according to the General Procedure A from **312a** (46 mg, 0.20 mmol) for a reaction time of 19 h and purified by column chromatography (hexane→15% EtOAc/hexane) to give a colourless oil (53 mg, 88%). IR (film) 2953, 1819, 1728 (C=O), 1435, 1283, 1251, 1066, 848, 762, 690 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.60-7.57 (2H, m, ArH), 7.46-7.40 (3H, m, ArH), 3.70 (6H, s, 2 x OCH₃), 0.35 (9H, s, Si(CH₃)₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 171.7 (2 x C), 130.2 (CH), 130.1 (2 x CH), 128.8 (2 x CH), 125.6 (C), 121.4 (C), 107.8 (C), 52.0 (2 x CH₃), 33.8 (C), -1.5 (3 x CH₃); HRMS (ES) Exact mass calcd for C₁₆H₂₁O₄Si [M+H]⁺: 305.1204, found: 305.1205.



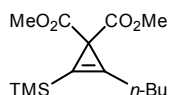
Dimethyl 2-(4-methylphenyl)-3-trimethylsilylcycloprop-2-ene-1,1-dicarboxylate (313b).

The title compound was prepared according to the General Procedure A from **312b** (49 mg, 0.20 mmol) for a reaction time of 44 h and purified by column chromatography (hexane→20% EtOAc/hexane) to give a colourless oil (57 mg, 90%). IR (film) 2953, 1817, 1730 (C=O), 1506, 1434, 1282, 1251, 1065, 848, 762 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.48 (2H, d, J = 8.1 Hz, ArH), 7.25 (2H, d, J = 8.1 Hz, ArH), 3.69 (6H, s, 2 x OCH_3), 2.40 (3H, s, ArCH₃), 0.34 (9H, s, Si(CH₃)₃); ^{13}C NMR (62.9 MHz, CDCl_3) δ 171.8 (2 x C), 140.6 (C), 130.1 (2 x CH), 129.6 (2 x CH), 122.7 (C), 121.2 (C), 106.3 (C), 52.0 (2 x CH₃), 33.7 (C), 21.6 (CH₃), -1.5 (3 x CH₃); HRMS (ES) Exact mass calcd for $\text{C}_{17}\text{H}_{23}\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^+$: 319.1360, found: 319.1361.



Dimethyl 2-(naphthalene-1-yl)-3-trimethylsilylcycloprop-2-ene-1,1-dicarboxylate (313c).

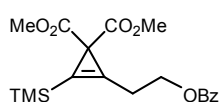
The title compound was prepared according to the General Procedure A from **312d** (56 mg, 0.20 mmol) for a reaction time of 44 h and purified by column chromatography (hexane→15% EtOAc/hexane) to give pale white crystals (54 mg, 76%). m.p 71-73 °C; IR (CHCl_3) 2952, 1809, 1731 (C=O), 1434, 1282, 1251, 1066, 844, 803, 774 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 8.46-8.43 (1H, m, ArH), 7.94-7.91 (2H, m, ArH), 7.73-7.52 (4H, m, ArH), 3.72 (6H, s, 2 x OCH_3), 0.46 (9H, s, Si(CH₃)₃); ^{13}C NMR (62.9 MHz, CDCl_3) δ 175.3 (2 x C), 141.9 (C), 129.8 (CH), 129.7 (C), 128.9 (2 x CH), 128.0 (2 x CH), 127.8 (CH), 127.1 (C), 126.1 (C), 125.9 (CH), 113.7 (C), 51.8 (2 x CH₃), 34.6 (C), -1.0 (3 x CH₃); HRMS (ES) Exact mass calcd for $\text{C}_{20}\text{H}_{23}\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^+$: 355.1360, found: 355.1357.



Dimethyl 2-butyl-3-trimethylsilylcycloprop-2-ene-1,1-dicarboxylate (313d).

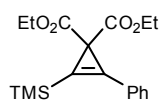
The title compound was prepared according to the General Procedure A from **312e** (43 mg, 0.20 mmol) for a reaction time of 44 h and purified by column chromatography (hexane→15% EtOAc/hexane) to give a colourless oil (56 mg, 99%). A similar experiment performed on ten times the scale

(ten times the quantity of reagents and solvent) provided 529 mg (93%) of **313d**. IR (film) 2956, 1836, 1726 (C=O), 1435, 1252, 1066, 847, 763, 637 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 3.66 (6H, s, 2 x OCH_3), 2.52 (2H, t, $J = 7.4$ Hz, $=\text{CCH}_2$), 1.62-1.54 (2H, m, CH_2), 1.43-1.33 (2H, m, CH_2), 0.90 (3H, t, $J = 7.3$ Hz, CH_2CH_3), 0.19 (9H, s, $\text{Si}(\text{CH}_3)_3$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 172.3 (2 x C), 123.6 (C), 103.9 (C), 51.8 (2 x CH_3), 33.6 (C), 28.8 (CH_2), 24.8 (CH_2), 22.1 (CH_2), 13.6 (CH_3), -1.7 (3 x CH_3); HRMS (ES) Exact mass calcd for $\text{C}_{14}\text{H}_{25}\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^+$: 285.1517, found: 285.1520.



Dimethyl 2-(2-benzoyloxyethyl)-3-trimethylsilylcycloprop-2-ene-1,1-dicarboxylate (313e).

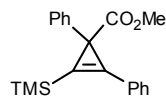
The title compound was prepared according to the General Procedure A from **312f** (61 mg, 0.20 mmol) for a reaction time of 44 h and purified by column chromatography (hexane \rightarrow 20% EtOAc/hexane) to give a colourless oil (52 mg, 69%). IR (film) 2954, 1840, 1723 (C=O), 1435, 1277, 1117, 1070, 847, 763, 714 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 8.04-8.01 (2H, m, ArH), 7.58-7.54 (1H, m, ArH), 7.46-7.41 (2H, m, ArH), 4.55 (2H, t, $J = 6.3$ Hz, CH_2O), 3.62 (6H, s, 2 x OCH_3), 3.05 (2H, t, $J = 6.3$ Hz, $=\text{CCH}_2$), 0.20 (9H, s, $\text{Si}(\text{CH}_3)_3$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 171.9 (2 x C), 166.3 (C), 133.0 (CH), 129.8 (C), 129.6 (2 x CH), 128.3 (2 x CH), 120.2 (C), 106.8 (C), 61.6 (CH_2), 51.9 (2 x CH_3), 33.4 (C), 25.2 (CH_2), -1.8 (3 x CH_3); HRMS (ES) Exact mass calcd for $\text{C}_{19}\text{H}_{25}\text{O}_6\text{Si}$ $[\text{M}+\text{H}]^+$: 377.1415, found: 377.1413.



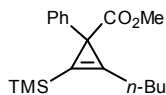
Diethyl 2-phenyl-3-trimethylsilylcycloprop-2-ene-1,1-dicarboxylate (313f).

The title compound was prepared according to the General Procedure A from **312g** (52 mg, 0.20 mmol) for a reaction time of 15 h and purified by column chromatography (hexane \rightarrow 15% EtOAc/hexane) to give a colourless oil (55 mg, 83%). IR (film) 2980, 1815, 1725 (C=O), 1447, 1366, 1251, 1061, 845, 761, 690 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.61-7.59 (2H, m, ArH), 7.46-7.39 (3H, m, ArH), 4.22-4.12 (4H, m, 2 x CH_2), 1.23 (6H, t, $J = 7.1$ Hz, 2 x CH_3), 0.35 (9H, s, $\text{Si}(\text{CH}_3)_3$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 171.3 (2 x C), 130.0 (3

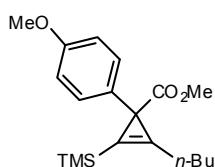
x CH), 128.7 (2 x CH), 125.8 (C), 121.8 (C), 107.7 (C), 60.7 (2 x CH₂), 34.2 (C), 14.2 (2 x CH₃), -1.4 (3 x CH₃); HRMS (ES) Exact mass calcd for C₁₈H₂₅O₄Si [M+H]⁺: 333.1517, found: 333.1517.



Methyl 1,2-diphenyl-3-trimethylsilylcycloprop-2-enecarboxylate (313g). The title compound was prepared according to the General Procedure A from **312h** (50 mg, 0.20 mmol) for a reaction time of 44 h and purified by column chromatography (hexane→15% EtOAc/hexane) to give a colourless oil (31 mg, 66%). IR (film) 2952, 1802, 1716 (C=O), 1490, 1250, 1205, 1021, 844, 758, 691 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.68-7.64 (2H, m, ArH), 7.51-7.39 (5H, m, ArH), 7.33-7.28 (2H, m, ArH), 7.24-7.19 (1H, m, ArH), 3.74 (3H, s, OCH₃), 0.35 (9H, s, Si(CH₃)₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 175.3 (C), 141.9 (C), 129.8 (2 x CH), 129.7 (CH), 128.9 (2 x CH), 128.0 (2 x CH), 127.8 (2 x CH), 127.1 (C), 126.1 (C), 125.9 (CH), 113.7 (C), 51.8 (CH₃), 34.6 (C), -1.0 (3 x CH₃); HRMS (ES) Exact mass calcd for C₂₀H₂₃O₂Si [M+H]⁺: 323.1462, found: 323.1463.



Methyl 2-butyl-1-phenyl-3-trimethylsilylcycloprop-2-enecarboxylate (313h). The title compound was prepared according to the General Procedure A from **312i** (46 mg, 0.20 mmol) for a reaction time of 16 h and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (41 mg, 68%). IR (film) 2957, 1822, 1716 (C=O), 1495, 1250, 1211, 1040, 844, 761, 698 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.28 (2H, br s, ArH), 7.27-7.26 (2H, m, PhH), 7.19-7.14 (1H, m, ArH), 3.66 (3H, s, OCH₃), 2.60 (2H, t, *J* = 7.3 Hz, =CCH₂), 1.67-1.58 (2H, m, CH₂), 1.46-1.34 (2H, m, CH₂), 0.92 (3H, t, *J* = 7.4 Hz, CH₂CH₃), 0.21 (9H, s, Si(CH₃)₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 176.2 (C), 142.8 (C), 130.1 (C), 128.1 (2 x CH), 127.8 (2 x CH), 125.6 (CH), 108.0 (C), 51.5 (CH₃), 34.5 (C), 29.3 (CH₂), 25.5 (CH₂), 22.3 (CH₂), 13.7 (CH₃), -1.0 (3 x CH₃); HRMS (ES) Exact mass calcd for C₁₈H₂₇O₂Si [M+H]⁺: 303.1775, found: 303.1773.

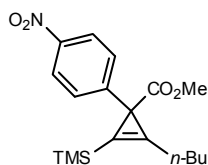


Methyl

2-butyl-1-(4-methoxyphenyl)-3-

trimethylsilylcycloprop-2-enecarboxylate (313i).

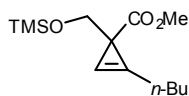
The title compound was prepared according to the General Procedure A from **312j** (52 mg, 0.20 mmol) for a reaction time of 26 h and purified by column chromatography (hexane→7.5% EtOAc/hexane) to give a colourless oil (56 mg, 84%). IR (film) 2956, 1822, 1715 (C=O), 1511, 1464, 1248, 1206, 1174, 1037, 842 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.22-7.18 (2H, m, ArH), 6.84-6.80 (2H, m, ArH), 3.79 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 2.60 (2H, t, $J = 7.1$ Hz, $=\text{CCH}_2$), 1.68-1.56 (2H, m, CH_2), 1.46-1.35 (2H, m, CH_2), 0.92 (3H, t, $J = 7.3$ Hz, CH_2CH_3), 0.21 (9H, s, $\text{Si}(\text{CH}_3)_3$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 176.5 (C), 157.6 (C), 135.1 (C), 130.5 (C), 129.2 (2 x CH), 113.3 (2 x CH), 108.4 (C), 55.2 (CH_3), 51.5 (CH_3), 33.8 (C), 29.3 (CH_2), 25.5 (CH_2), 22.3 (CH_2), 13.7 (CH_3), -1.0 (3 x CH_3); HRMS (ES) Exact mass calcd for $\text{C}_{19}\text{H}_{32}\text{NO}_3\text{Si}$ $[\text{M}+\text{NH}_4]^+$: 350.2146, found: 350.2147.



Methyl 2-butyl-1-(4-nitrophenyl)-3-trimethylsilylcycloprop-2-

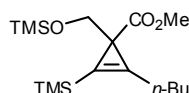
enecarboxylate (313j).

The title compound was prepared according to the General Procedure A from **312k** (55 mg, 0.20 mmol) for a reaction time of 19 h and purified by column chromatography (hexane→10% EtOAc/hexane) to give a yellow oil (55 mg, 80%). IR (film) 2957, 1828, 1714 (C=O), 1596, 1516, 1346, 1286, 1199, 852, 705 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 8.14-8.10 (2H, m, ArH), 7.50-7.46 (2H, m, ArH), 3.68 (3H, s, OCH_3), 2.58 (2H, td, $J = 7.3, 2.4$ Hz, $=\text{CCH}_2$), 1.65-1.56 (2H, m, CH_2), 1.45-1.35 (2H, m, CH_2), 0.92 (3H, t, $J = 7.3$ Hz, CH_2CH_3), 0.20 (9H, s, $\text{Si}(\text{CH}_3)_3$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 174.7 (C), 151.1 (C), 145.6 (C), 128.4 (2 x CH), 127.9 (C), 123.0 (2 x CH), 107.4 (C), 51.7 (CH_3), 34.4 (C), 29.2 (CH_2), 25.1 (CH_2), 22.2 (CH_2), 13.6 (CH_3), -1.2 (3 x CH_3); HRMS (EI) Exact mass calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_4\text{Si}$ $[\text{M}]^+$: 347.1547, found: 347.1545.



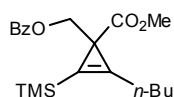
Methyl 2-butyl-1-trimethylsilyloxymethylcycloprop-2-ene-1-carboxylate (315).

The title compound was prepared according to the General Procedure A from **314** (37 mg, 0.20 mmol) for a reaction time of 18 h and purified by column chromatography (hexane→15% EtOAc/hexane) to give a colourless oil (48 mg, 93%) that displayed identical spectroscopic data to those reported on page 132.



Methyl 2-butyl-3-trimethylsilyl-1-(trimethylsilyloxy)cycloprop-2-ene-1-carboxylate (316).

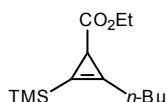
The title compound was prepared according to the General Procedure A, but with a modification of the quantities of reactant/reagents used [cyclopropene **315** (41 mg, 0.16 mmol), Cu(acac)₂ (2.1 mg, 0.008 mmol), dppe (3.2 mg, 0.008 mmol) and TMSCF₃ (47 μL, 0.32 mmol) in THF (0.7 mL)] for a reaction time of 16 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (10 mg, 18%). IR (film) 2790, 1820, 1722 (C=O), 1586, 1529, 1249, 1061, 843, 630, 515 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 3.90 (1H, d, *J* = 10.5 Hz, OCH₂), 3.77 (1H, d, *J* = 10.5 Hz, OCH₂), 3.60 (3H, s, OCH₃), 2.50 (2H, t, *J* = 7.3 Hz, =CCH₂), 1.62-1.54 (2H, m, CH₂), 1.45-1.35 (2H, m, CH₂), 0.93 (3H, t, *J* = 7.3 Hz, CH₂CH₃), 0.18 (9H, s, Si(CH₃)₃), 0.08 (9H, s, Si(CH₃)₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 177.0 (C), 129.5 (C), 106.7 (C), 65.6 (CH₂), 51.2 (CH₃), 32.9 (C), 29.4 (CH₂), 25.9 (CH₂), 22.3 (CH₂), 13.8 (CH₃), -0.5 (3 x (CH₃)₃), -1.2 (3 x CH₃); HRMS (ES) Exact mass calcd for C₁₆H₃₃O₃Si₂ [M+H]⁺: 329.1963, found: 329.1965.



Methyl 1-benzoyloxymethyl-2-butyl-3-trimethylsilylcycloprop-2-ene-1-carboxylate (318).

The title compound was prepared according to the General Procedure B from **317** (58 mg, 0.20 mmol) for a reaction time of 22 h and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (18 mg, 24%). IR (film) 2956, 1829, 1718 (C=O), 1452, 1273, 1250, 1109, 1069, 844, 713 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.06-8.02 (2H, m, ArH), 7.58-7.53 (1H, m, ArH), 7.46-7.41 (2H, m, ArH), 4.66 (1H, d, *J* = 11.4 Hz, OCH₂), 4.49 (1H, d, *J* = 11.4 Hz, OCH₂), 3.66 (3H, s, OCH₃), 2.55 (2H, t, *J*

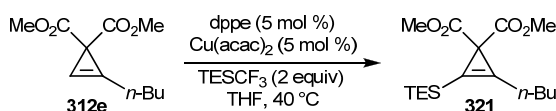
= 7.4 Hz, =CCH₂), 1.64-1.55 (2H, m, CH₂), 1.45-1.34 (2H, m, CH₂), 0.91 (3H, t, *J* = 7.3 Hz, CH₂CH₃), 0.20 (9H, s, Si(CH₃)₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 175.9 (C), 166.6 (C), 132.7 (CH), 130.6 (C), 129.6 (2 x CH), 129.4 (C), 128.3 (2 x CH), 107.1 (C), 69.8 (CH₂), 51.6 (CH₃), 29.8 (C), 29.3 (CH₂), 25.8 (CH₂), 22.3 (CH₂), 13.7 (CH₃), -1.3 (3 x CH₃).



Ethyl 2-butyl-3-trimethylsilylcycloprop-2-ene-1-carboxylate (320).

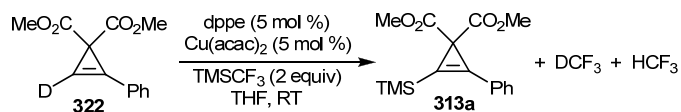
The title compound was prepared according to the General Procedure A from **319** (34 mg, 0.20 mmol) for a reaction time of 20 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (9 mg, 19%) that showed spectroscopic data consistent with those reported previously.¹²¹

Dimethyl 2-butyl-3-triethylsilylcycloprop-2-ene-1,1-dicarboxylate (321).



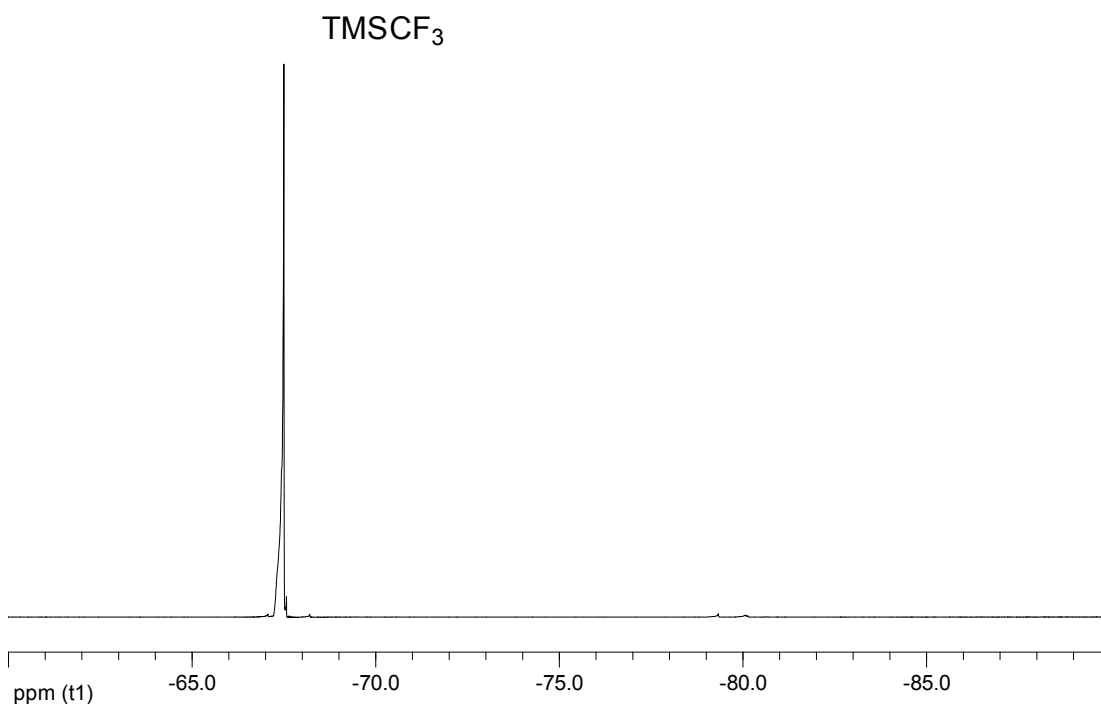
A solution of cyclopropene **312e** (43 mg, 0.20 mmol), Cu(acac)₂ (2.6 mg, 0.01 mmol) and dppe (4.0 mg, 0.01 mmol) in THF (0.7 mL) was stirred at room temperature for 30 min. TESCF₃ (75 μL, 0.40 mmol) was then added in one portion and the reaction was stirred at 40 °C for 21 h. The reaction mixture was filtered through a short plug of SiO₂ (*ca.* 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→10% EtOAc/hexane) gave the *silylated cyclopropene* **321** (11 mg, 16%) as a colourless oil. IR (film) 2955, 1725 (C=O), 1460, 1434, 1379, 1237, 1066, 1018, 833, 741 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 3.67 (6H, s, 2 x OCH₃), 2.57 (2H, t, *J* = 7.4 Hz, =CCH₂), 1.62-1.54 (2H, m, CH₂), 1.44-1.34 (2H, m, CH₂), 0.97 (9H, t, *J* = 7.7 Hz, Si(CH₂CH₃)₃), 0.92 (3H, t, *J* = 7.4 Hz, CH₂CH₃), 0.70 (6H, q, *J* = 7.7 Hz, Si(CH₂CH₃)₂); ¹³C NMR (62.9 MHz, CDCl₃) δ 172.5 (2 x C), 124.9 (C), 102.1 (C), 51.7 (CH₃), 29.7 (C), 28.7 (CH₂), 25.1 (CH₂), 22.2 (CH₂), 13.6 (CH₃), 7.0 (3 x CH₃), 3.4 (3 x CH₂); HRMS (ES) Exact mass calcd for C₁₇H₃₁O₄Si [M+H]⁺: 327.1986, found: 327.1984.

¹⁹F NMR Experiments

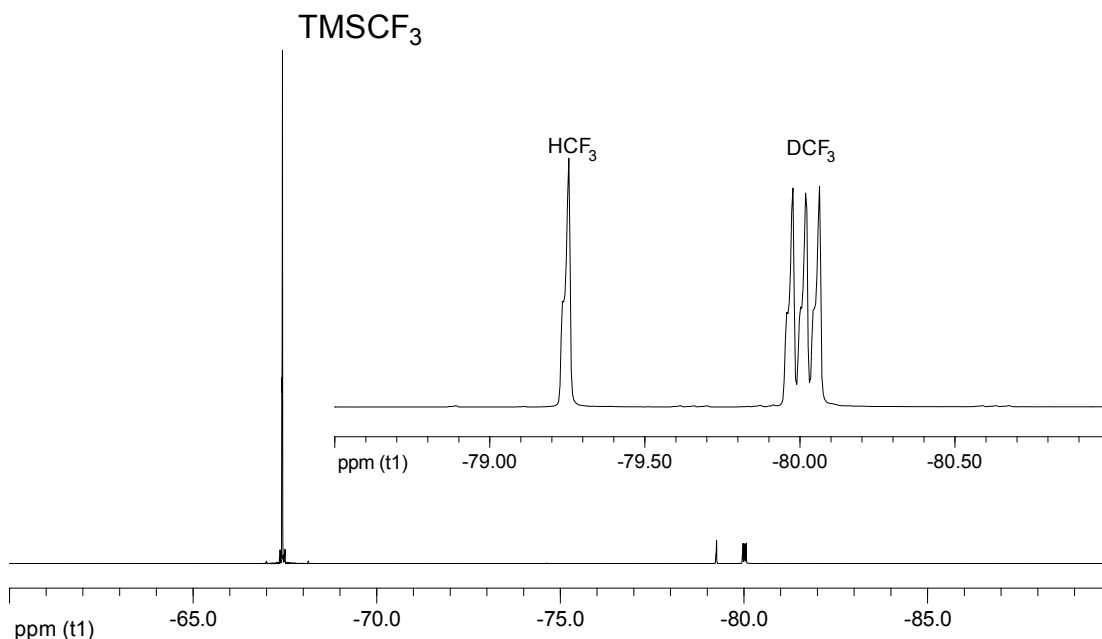


In an NMR tube, a solution of deuterated cyclopropene **322** (46.6 mg, 0.20 mmol), Cu(acac)₂ (2.6 mg, 0.01 mmol), dppe (4.0 mg, 0.01 mmol), and C₆F₆ (internal standard: 2.3 μL, 0.02 mmol) in THF (0.7 mL) under argon was stirred at room temperature for 30 min. TMSCF₃ (59 μL, 0.40 mmol) was then added in one portion, and the reaction was followed by ¹⁹F NMR spectroscopy. As the reaction progressed, both DCF₃ (δ -80 ppm, t, *J*_{FD} = 12.1 Hz) and HCF₃ were detected in the mixture, though the silylation did not proceed to completion on this occasion.

¹⁹F NMR spectrum after 2 min:



¹⁹F NMR spectrum after 9 h:



EPR Experiments

A solution of $\text{Cu}(\text{acac})_2$ (6.5 mg, 0.025 mmol) and dppe (10.0 mg, 0.025 mmol) in THF (1.75 mL) was stirred at room temperature for 30 min. The mixture was transferred to a quartz flat cell and the solution EPR spectrum was acquired. A copper hyperfine coupling constant (A^{Cu}) of 70 G and spectroscopic splitting factor (g) of 2.13365 were obtained. The experiment was repeated with the same quantities, but after stirring $\text{Cu}(\text{acac})_2$ and dppe in THF for 30 min, TMSCF_3 (148 μL , 1.00 mmol) was added, and the mixture was stirred at room temperature for 40 min until a colour change to blue/grey and then to green was observed. The EPR spectrum of this mixture was acquired, and values identical to those observed previously for the copper hyperfine constant (A^{Cu}) and spectroscopic splitting factor (g) were obtained.

Cyclic Voltammetry Experiments

$\text{Cu}(\text{acac})_2$ (2.6 mg, 0.01 mmol) was dissolved in 0.1 M tetrabutylammonium tetrafluoroborate in THF (5 mL) in the three electrode cell, and the solution was degassed by flushing with nitrogen. The cell was initially scanned to positive potential in order to detect any $\text{Cu}(\text{I}) \rightarrow \text{Cu}(\text{II})$ oxidation. No oxidation potential was

observed. The cell was then scanned to negative potential (Figure 1). This sequence of degassing, scanning to positive potential and then to negative potential was repeated: (i) after the addition of dppe (4.0 mg, 0.01 mmol); (ii) after the addition of cyclopropene **312e** (43 mg, 0.20 mmol), and (iii) finally after the addition of TMSCF_3 (59 μL , 0.40 mmol). In the latter case a period of *ca.* 30 min was allowed to elapse until the mixture turned green. In each case no oxidation potential was observed on scanning to positive potentials. $\text{Cu(II)} \rightarrow \text{Cu(I)}$ reduction potentials (~ -1.0 V) were observed on scanning to negative potential, as were the resulting $\text{Cu(I)} \rightarrow \text{Cu(II)}$ oxidation potentials (0.25 \rightarrow 0.75 V) on scanning to positive potential. From these results we suggest that the copper species in solution remains in the +2 oxidation state and is not reduced upon the addition of TMSCF_3 . The changes in the values of oxidation potentials observed after the addition of dppe and TMSCF_3 also suggest the formation of distinct copper complexes.

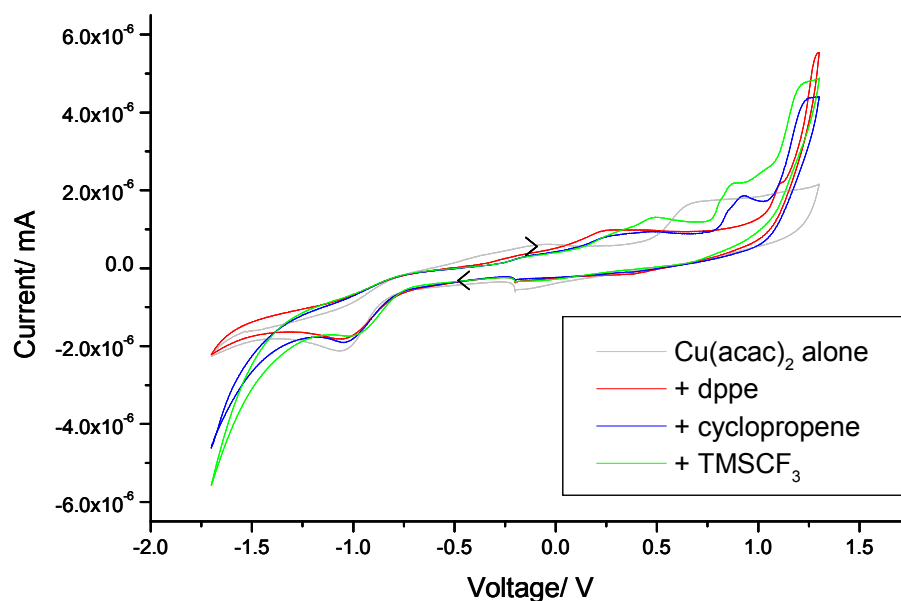
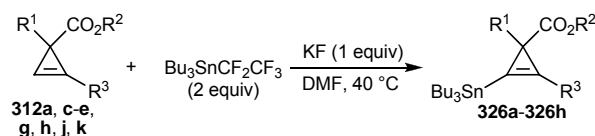
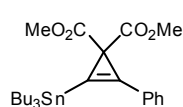


Figure 1

Stannylation of Cyclopropenes: General Procedure C

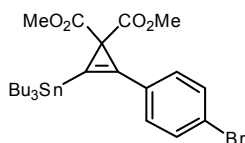


A solution of the appropriate cyclopropene (0.20 mmol), KF (11.6 mg, 0.20 mmol), and $\text{Bu}_3\text{SnCF}_2\text{CF}_3$ (164 mg, 0.40 mmol) in DMF (0.8 mL) was stirred at 40 °C until complete consumption of the cyclopropene as observed by TLC analysis, or until no further reaction progress could be seen. After cooling to room temperature, the reaction mixture was filtered through a short plug of SiO_2 (*ca.* 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/hexane) afforded the stannylated product.



Dimethyl 2-phenyl-3-tributylstannylcycloprop-2-ene-1,1-dicarboxylate (326a).

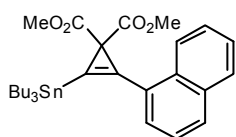
The title compound was prepared according to General Procedure C from **312a** (46 mg, 0.20 mmol) for a reaction time of 20 h and purified by column chromatography (heptane→7.5% EtOAc/heptane) to give a colourless oil (85 mg, 82%). IR (film) 2953, 2922, 1721 (C=O), 1489, 1433, 1278, 1231, 1062, 760, 689 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.58-7.54 (2H, m ArH), 7.45-7.34 (3H, m, ArH), 3.69 (6H, s, 2 x OCH_3), 1.70-1.55 (6H, m, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$), 1.43-1.31 (6H, m, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$), 1.24-1.18 (6H, m, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$), 0.93 (9H, t, $J = 7.3$ Hz, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 171.3 (2 x C), 129.0 (CH), 128.8 (2 x CH), 128.1 (2 x CH), 125.7 (C), 123.2 (C), 108.5 (C), 52.2 (2 x CH_3), 34.2 (C), 29.4 ($J_{\text{Sn-C}} = 11.1$ Hz, 3 x CH_2), 27.7 ($J_{\text{Sn-C}} = 30.0$ Hz, 3 x CH_2), 14.4 (3 x CH_3), 12.0 ($J_{\text{Sn-C}} = 179.6, 171.6$ Hz, 3 x CH_2); HRMS (ES) Exact mass calcd for $\text{C}_{25}\text{H}_{39}\text{O}_4^{120}\text{Sn}$ $[\text{M}+\text{H}]^+$: 523.1866, found: 523.1864.



Dimethyl 2-(4-bromophenyl)-3-tributylstannylcycloprop-2-ene-1,1-dicarboxylate (326b).

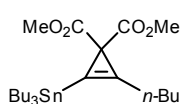
The title compound was

prepared according to General Procedure C from **312c** (62 mg, 0.20 mmol) for a reaction time of 19 h and purified by column chromatography (heptane→7.5% ethyl acetate/heptane) to give a colourless oil (76 mg, 63%). IR (film) 2954, 2924, 2853, 1732 (C=O), 1481, 1434, 1243, 1067, 1011, 826 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.56 (2H, dm, $J = 8.4$ Hz, ArH), 7.42 (2H, dm, $J = 8.4$ Hz, ArH), 3.69 (6H, s, 2 x OCH_3), 1.70-1.55 (6H, m, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$), 1.42-1.28 (6H, m, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$), 1.30-1.09 (6H, m, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$), 0.92 (9H, t, $J = 7.3$ Hz, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 172.3 (2 x C), 132.1 (2 x CH), 130.8 (2 x CH), 125.4 (C), 123.9 (C), 123.1 (C), 110.3 (C), 52.0 (2 x CH_3), 33.7 (C), 28.8 ($J_{\text{Sn-C}} = 11.2$ Hz, 3 x CH_2), 27.1 ($J_{\text{Sn-C}} = 30.0$ Hz, 3 x CH_2), 13.6 (3 x CH_3), 11.2 ($J_{\text{Sn-C}} = 181.6, 173.6$ Hz, 3 x CH_2); HRMS (ES) Exact mass calcd for $\text{C}_{25}\text{H}_{38}^{79}\text{BrO}_4^{120}\text{Sn} [\text{M}+\text{H}]^+$: 601.0970, found: 601.0978.



Dimethyl 2-(naphthalen-1-yl)-3-tributylstannylcycloprop-2-ene-1,1-dicarboxylate (326c). The title compound was prepared according to General Procedure C from **312d** (57 mg, 0.20

mmol) for a reaction time of 23 h and purified by column chromatography (hexane→7.5% ethyl acetate/hexane) to give a pale yellow oil (64 mg, 56%). IR (film) 2954, 2925, 2852, 1728 (C=O), 1508, 1462, 1433, 1279, 1234, 1066 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 8.43-8.40 (1H, m, ArH), 7.93-7.88 (2H, m, ArH), 7.68-7.51 (4H, m, ArH), 3.70 (6H, s, 2 x OCH_3), 1.68-1.59 (6H, m, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$), 1.42-1.32 (6H, m, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$), 1.31-1.27 (6H, m, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$), 0.90 (9H, t, $J = 7.3$ Hz, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 172.6 (2 x C), 133.5 (C), 132.0 (C), 130.2 (CH), 129.9 (CH), 128.6 (CH), 126.7 (CH), 126.3 (CH), 125.7 (CH), 124.7 (CH), 122.9 (C), 121.3 (C), 111.1 (C), 51.9 (2 x CH_3), 32.0 (C), 28.8 ($J_{\text{Sn-C}} = 10.9$ Hz, 3 x CH_2), 27.2 ($J_{\text{Sn-C}} = 31.9$ Hz, 3 x CH_2), 13.6 (3 x CH_3), 11.3 ($J_{\text{Sn-C}} = 181.8, 171.0$ Hz, 3 x CH_2); HRMS (ES) Exact mass calcd for $\text{C}_{29}\text{H}_{40}\text{O}_4^{120}\text{Sn} [\text{M}+\text{H}]^+$: 573.2027, found: 573.2026.

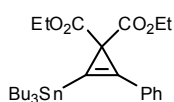


Dimethyl

2-butyl-3-tributylstannylcycloprop-2-ene-1,1-

dicarboxylate (326d).

The title compound was prepared according to General Procedure C from **312e** (43 mg, 0.20 mmol) for a reaction time of 15 hours and purified by column chromatography (heptane→7.5% ethyl acetate/heptane) to give a colourless oil (87 mg, 87%). IR (film) 2956, 2930, 1719 (C=O), 1465, 1433, 1275, 1225, 1063, 832, 746 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 3.66 (6H, s, 2 x OCH_3), 2.55 (2H, t, $J = 7.3$ Hz, $=\text{CCH}_2$), 1.63-1.49 (8H, m, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$ and $=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.44-1.26 (8H, m, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$ and $=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.19-0.96 (6H, m, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$), 0.92 (3H, t, $J = 7.2$ Hz, $=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.91 (9H, t, $J = 7.2$ Hz, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 172.1 (2 x C), 124.8 (C), 103.1 (C), 51.9 (2 x CH_3), 34.0 (C), 29.4 ($J_{\text{Sn-C}} = 11.1$ Hz, 3 x CH_2), 27.7 ($J_{\text{Sn-C}} = 29.6$ Hz, 3 x CH_2), 25.7 (CH_2), 22.9 (CH_2), 14.5 (CH_3), 14.4 (3 x CH_3), 11.6 ($J_{\text{Sn-C}} = 179.8, 171.8$ Hz, 3 x CH_2); HRMS (ES) Exact mass calcd for $\text{C}_{23}\text{H}_{43}\text{O}_4^{120}\text{Sn}$ $[\text{M}+\text{H}]^+$: 503.2177, found: 503.2178.

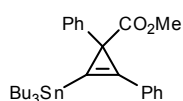


Diethyl

2-phenyl-3-tributylstannylcycloprop-2-ene-1,1-

dicarboxylate (326e).

The title compound was prepared according to General Procedure C from **312g** (52 mg, 0.20 mmol) for a reaction time of 22 h and purified by column chromatography (hexane→10% EtOAc/hexane) to give a pale yellow oil (75 mg, 69%). IR (film) 2957, 2927, 2871, 1723 (C=O), 1597, 1446, 1365, 1275, 1061, 876 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.59-7.57 (2H, m, ArH), 7.44-7.33 (3H, m, ArH), 4.20-4.11 (4H, m, 2 x OCH_2), 1.71-1.57 (6H, m, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$), 1.41-1.31 (6H, m, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$), 1.29-1.10 (6H, m, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$), 1.22 (6H, t, $J = 7.1$ Hz, 2 x OCH_2CH_3), 0.91 (9H, t, $J = 7.3$ Hz, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 172.2 (2 x C), 129.4 (3 x CH), 128.7 (2 x CH), 126.6 (C), 124.3 (C), 108.8 (C), 60.5 (2 x CH_2), 34.1 (C), 28.8 ($J_{\text{Sn-C}} = 11.1$ Hz, 3 x CH_2), 27.1 ($J_{\text{Sn-C}} = 29.8$ Hz, 3 x CH_2), 14.2 (2 x CH_3), 13.6 (3 x CH_3), 11.1 ($J_{\text{Sn-C}} = 181.7, 173.9$ Hz, 3 x CH_2); HRMS (ES) Exact mass calcd for $\text{C}_{27}\text{H}_{42}\text{O}_4\text{Na}^{120}\text{Sn}$ $[\text{M}+\text{Na}]^+$: 573.1997, found: 573.2008.

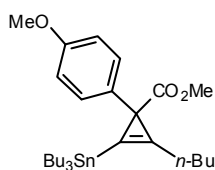


Methyl

1,2-diphenyl-3-tributylstannylcycloprop-2-

enecarboxylate (326f).

The title compound was prepared according to General Procedure C from **312h** (50 mg, 0.20 mmol) for a reaction time of 16 h and purified by column chromatography (hexane→10% EtOAc/hexane) to give a pale yellow oil (70 mg, 65%). IR (film) 2955, 2928, 2871, 2853, 1715 (C=O), 1488, 1284, 1199, 759, 691 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.62-7.59 (2H, m, ArH), 7.46-7.34 (5H, m, ArH), 7.27-7.22 (2H, m, ArH), 7.18-7.13 (1H, m, ArH), 3.69 (3H, s, OCH₃), 1.60-1.49 (6H, m, Sn(CH₂CH₂CH₂CH₃)₃), 1.36-1.26 (6H, m, Sn(CH₂CH₂CH₂CH₃)₃), 1.23-1.04 (6H, m, Sn(CH₂CH₂CH₂CH₃)₃), 0.88 (9H, t, J = 7.3 Hz, Sn(CH₂CH₂CH₂CH₃)₃); ^{13}C NMR (62.9 MHz, CDCl_3) δ 176.1 (C), 143.1 (C), 129.1 (2 x CH and C), 128.8 (2 x CH), 128.0 (2 x CH), 127.8 (CH), 127.7 (2 x CH and C), 125.6 (CH), 115.2 (C), 51.6 (CH₃), 34.2 (C), 28.9 ($J_{\text{Sn-C}}$ = 11.1 Hz, 3 x CH₂), 27.1 ($J_{\text{Sn-C}}$ = 29.8 Hz, 3 x CH₂), 13.6 (3 x CH₃), 11.1 ($J_{\text{Sn-C}}$ = 180.7, 172.8 Hz, 3 x CH₂); HRMS (ES) Exact mass calcd for C₂₉H₄₁O₂¹²⁰Sn [M+H]⁺: 541.2123, found: 541.2104.



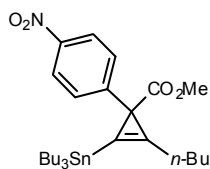
Methyl

2-butyl-1-(4-methoxyphenyl)-3-

tributylstannylcycloprop-2-enecarboxylate (326g).

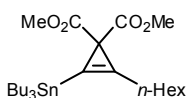
The title compound was prepared according to General Procedure C from **312j** (52 mg, 0.20 mmol) for a reaction time of 19.5 h and purified by column chromatography (hexane→7.5% EtOAc/hexane) to give a colourless oil (69 mg, 63%). IR (film) 2956, 1711 (C=O), 1510, 1464, 1246, 1200, 1173, 1033, 909, 733 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.19 (2H, dm, J = 8.8 Hz, ArH), 6.80 (2H, dm, J = 8.8 Hz, ArH), 3.79 (3H, s OCH₃), 3.63 (3H, s OCH₃), 2.60 (2H, t, J = 7.3 Hz, =CCH₂), 1.61-1.55 (2H, m, =CCH₂CH₂), 1.52-1.46 (6H, m, Sn(CH₂CH₂CH₂CH₃)₃), 1.42-1.34 (2H, m, =CCH₂CH₂CH₂), 1.33-1.26 (6H, m, Sn(CH₂CH₂CH₂CH₃)₃), 1.10-0.97 (6H, m, Sn(CH₂CH₂CH₂CH₃)₃), 0.91 (3H, t, J = 7.4 Hz, =CCH₂CH₂CH₂CH₃), 0.88 (9H, t, J = 7.3 Hz, Sn(CH₂CH₂CH₂CH₃)₃); ^{13}C NMR (62.9 MHz, CDCl_3) δ 177.4 (C), 157.3 (C), 136.3 (C), 131.5 (C), 129.0 (2 x CH), 113.1 (2 x CH), 107.8 (C), 55.2 (CH₃), 51.4 (CH₃), 33.1 (C), 29.2 (CH₂), 28.9 ($J_{\text{Sn-C}}$ = 11.0 Hz, 3 x CH₂), 27.1 ($J_{\text{Sn-C}}$ = 29.8 Hz, 3 x CH₂), 25.6 (CH₂), 22.4 (CH₂),

13.8 (CH₃), 13.6 (3 x CH₃), 10.8 ($J_{\text{Sn-C}} = 180.8, 172.8$ Hz, 3 x CH₂); HRMS (FAB) Exact mass calcd for C₂₈H₄₇O₃¹²⁰Sn [M+H]⁺: 551.2542, found: 551.2563.



Methyl 2-butyl-1-(4-nitrophenyl)-3-tributylstannylcycloprop-2-enecarboxylate (326h). The title compound was prepared according to General Procedure C from **312k** (55 mg, 0.20 mmol) for a reaction time of 20 h and purified by column chromatography

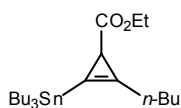
(hexane→7.5% EtOAc/hexane) to give a pale yellow oil (99 mg, 88%). IR (film) 2957, 2930, 1706 (C=O), 1594, 1514, 1345, 1286, 1198, 909, 734 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.11 (2H, dm, $J = 9.0$ Hz, ArH), 7.49 (2H, dm, $J = 9.0$ Hz, ArH), 3.66 (3H, s, OCH₃), 2.58 (2H, t, $J = 7.3$ Hz, =CCH₂), 1.58-1.52 (2H, m, =CCH₂CH₂), 1.50-1.43 (6H, m, Sn(CH₂CH₂CH₂CH₃)₃), 1.41-1.34 (2H, m, =CCH₂CH₂CH₂), 1.31-1.24 (6H, m, Sn(CH₂CH₂CH₂CH₃)₃), 1.10-0.96 (6H, m, Sn(CH₂CH₂CH₂CH₃)₃), 0.90 (3H, t, $J = 7.3$ Hz, =CCH₂CH₂CH₂CH₃), 0.86 (9H, t, $J = 7.3$ Hz, Sn(CH₂CH₂CH₂CH₃)₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 175.6 (C), 152.7 (C), 145.3 (C), 128.8 (C), 128.2 (2 x CH), 122.9 (2 x CH), 107.0 (C), 51.6 (CH₃), 34.0 (C), 29.1 (CH₂), 28.8 ($J_{\text{Sn-C}} = 11.2$ Hz, 3 x CH₂), 27.1 ($J_{\text{Sn-C}} = 30.0$ Hz, 3 x CH₂), 25.2 (CH₂), 22.3 (CH₂), 13.7 (CH₃), 13.6 (3 x CH₃), 11.0 ($J_{\text{Sn-C}} = 180.7, 172.2$ Hz, 3 x CH₂); HRMS (FAB) Exact mass calcd for C₂₇H₄₄O₄N¹²⁰Sn [M+H]⁺: 566.2287, found: 566.2287.



Dimethyl 2-hexyl-3-tributylstannylcycloprop-2-ene-1,1-dicarboxylate (326i). The title compound as prepared according to

General Procedure C, but with modification of the quantities of reactant/reagents used [cyclopropene **312l** (192 mg, 0.80 mmol), KF (47 mg, 0.80 mmol), and Bu₃SnCF₃ (575 mg, 1.60 mmol) in DMF (3.2 mL)] for a reaction time of 17 h and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (222 mg, 52%). IR (film) 2956, 2930, 2855, 1723 (C=O), 1462, 1434, 1281, 1069, 911, 734 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 3.66 (6H, s, 2 x OCH₃), 2.54 (2H, t, $J = 7.3$ Hz, =CCH₂), 1.60-1.50 (8H, m, Sn(CH₂CH₂CH₂CH₃)₃ and =CCH₂CH₂), 1.36-1.26 (12H, m, Sn(CH₂CH₂CH₂CH₃)₃ and CH₂(CH₂)₃CH₃),

1.09-1.05 (6H, m, Sn(CH₂CH₂CH₂CH₃)₃), 0.92 (9H, t, J = 7.3 Hz, Sn(CH₂CH₂CH₂CH₃)₃), 0.89 (3H, t, J = 7.1 Hz, (CH₂)₅CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 173.2 (2 x C), 125.4 (C), 103.4 (C), 51.6 (2 x CH₃), 33.4 (C), 31.5 (CH₂), 28.8 (CH₂), 28.8 ($J_{\text{Sn-C}}$ = 11.0 Hz, 3 x CH₂), 27.0 ($J_{\text{Sn-C}}$ = 29.4 Hz, 3 x CH₂), 26.6 (CH₂), 25.3 (CH₂), 22.5 (CH₂), 14.0 (CH₃), 13.6 (3 x CH₃), 10.8 ($J_{\text{Sn-C}}$ not observable, 3 x CH₂).

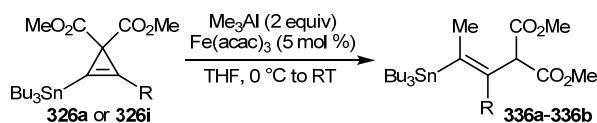


Ethyl 2-butyl-3-tributylstannylcycloprop-2-ene-1-carboxylate

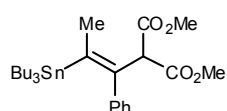
(329). The title compound was prepared according to General

Procedure C from **319** (34 mg, 0.20 mmol) for a reaction time of 24 h and purified by column chromatography (hexane→6% EtOAc/hexane) to give a pale yellow oil (26 mg, 29%). IR (film) 2957, 2929, 2871, 1716 (C=O), 1463, 1330, 1234, 1173, 1042, 876 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 4.15-4.02 (2H, m, OCH₂CH₃), 2.53 (2H, t, J = 7.3 Hz, =CCH₂), 1.92 (1H, s, CHCO₂CH₂CH₃), 1.60-1.50 (8H, m, Sn(CH₂CH₂CH₂CH₃)₃ and =CCH₂CH₂), 1.41-1.27 (8H, m, Sn(CH₂CH₂CH₂CH₃)₃ and =CCH₂CH₂CH₂), 1.22 (3H, t, J = 7.1 Hz, OCH₂CH₃), 1.13-0.96 (6H, m, Sn(CH₂CH₂CH₂CH₃)₃), 0.92 (3H, t, J = 7.4 Hz, =CH₂CH₂CH₂CH₃), 0.90 (9H, t, J = 7.3 Hz, Sn(CH₂CH₂CH₂CH₃)₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 178.2 (C), 128.7 (C), 102.7 (C), 59.6 (CH₂), 29.0 (CH₂), 28.9 ($J_{\text{Sn-C}}$ = 11.2 Hz, 3 x CH₂), 27.1 ($J_{\text{Sn-C}}$ = 28.3 Hz, 3 x CH₂), 26.3 (CH₂), 22.3 (CH₂), 21.2 (CH), 14.5 (CH₃), 13.8 (CH₃), 13.6 (3 x CH₃), 10.6 ($J_{\text{Sn-C}}$ = 181.5, 173.6 Hz, 3 x CH₂); HRMS (ES) Exact mass calcd for C₂₂H₄₂O₂Na¹²⁰Sn [M+Na]⁺: 481.2099, found: 481.2075.

Iron-Catalyzed Carbometalation Ring-Opening Reactions: General Procedure D

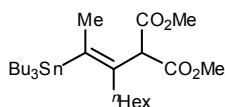


To a solution of the appropriate cyclopropene (0.10 mmol) and $\text{Fe}(\text{acac})_3$ (1.8 mg, 0.005 mmol) in THF (1 mL) at 0 °C was added Me_3Al (2.0 M in hexanes, 0.1 mL, 0.20 mmol) dropwise over 1 min. The reaction was stirred at 0 °C for 1 h and then room temperature for 15 h, diluted with CH_2Cl_2 (5 mL) and poured into saturated aqueous Rochelle's salt solution (10 mL). The mixture was stirred vigorously for 30 min and the aqueous layer was then separated and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography gave the alkene product.



(Z)-Dimethyl 2-[1-phenyl-2-(tributylstannyl)prop-1-enyl]malonate (336a). The title compound was prepared according to the General Procedure D from cyclopropene **326a**

(52 mg, 0.10 mmol) and Me_3Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (44 mg, 82%). IR (film) 2954, 2924, 2853, 1740 (C=O), 1436, 1310, 1147, 1034, 911, 734 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.26-7.21 (5H, m, ArH), 4.88 (1H, s, =CCH), 3.58 (6H, s, 2 x OCH_3), 1.95 (3H, s, $\text{CH}_3\text{C=}$), 1.33-1.26 (6H, m, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$), 1.24-1.16 (6H, m, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$), 0.84 (9H, t, $J = 7.2$ Hz, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$), 0.53-0.49 (6H, m, $\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_3$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 168.8 (2 x C), 145.9 (C), 143.2 (C), 140.9 (C), 129.6 (2 x CH), 127.8 (2 x CH), 127.2 (CH), 55.8 (CH), 52.3 (2 x CH_3), 29.0 ($J_{\text{Sn-C}} = 9.5$ Hz, 3 x CH_2), 27.3 ($J_{\text{Sn-C}} = 30.6$ Hz, 3 x CH_2), 21.6 (CH_3), 13.6 (3 x CH_3), 10.4 ($J_{\text{Sn-C}} = 167.6, 160.5$ Hz, 3 x CH_2); HRMS (FAB) Exact mass calcd for $\text{C}_{26}\text{H}_{43}\text{O}_4^{120}\text{Sn}$ [$\text{M}+\text{H}$] $^+$: 539.2178, found: 539.2186.



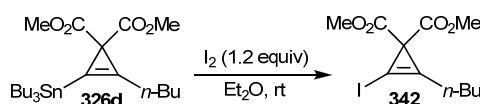
(E)-Dimethyl

2-[1-(1-

tributylstannylethylidene)heptyl]malonate (336b). The title

compound was prepared according to the General Procedure D from cyclopropene **326i** (53 mg, 0.10 mmol) and Me₃Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a 10:1 inseparable mixture of regioisomers as a colourless oil (38 mg, 70%). IR (film) 2955, 2926, 2854, 1738 (C=O), 1601, 1435, 1146, 1037, 910, 734 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 4.54 (1H, s, =CCH), 3.73 (6H, s, CO₂CH₃), 2.11-2.08 (2H, m, =CCH₂), 1.83 (3H, s, CH₃C=), 1.51-1.43 (6H, m, Sn(CH₂CH₂CH₂CH₃)₃), 1.35-1.25 (14H, m, Sn(CH₂CH₂CH₂CH₃)₃ and (CH₂)₄CH₃), 0.95-0.86 (18H, m, Sn(CH₂CH₂CH₂CH₃)₃ and (CH₂)₅CH₃), ¹³C NMR (62.9 MHz, CDCl₃) δ 169.2 (2 x C), 141.0 (C), 139.0 (C), 53.8 (CH), 52.3 (2 x CH₃), 40.3 (CH₂), 31.8 (CH₂), 30.1 (CH₂), 29.7 (CH₂), 29.1 (*J*_{Sn-C} = 9.5 Hz, 3 x CH₂), 27.4 (*J*_{Sn-C} = 29.0 Hz, 3 x CH₂), 22.6 (CH₂), 21.5 (CH₃), 14.0 (CH₃), 13.7 (3 x CH₃), 10.7 (*J*_{Sn-C} = 164.6, 157.3 Hz, 3 x CH₂); HRMS (FAB) Exact mass calcd for C₂₆H₅₁O₄¹²⁰Sn [M+H]⁺: 547.2804, found: 547.2790.

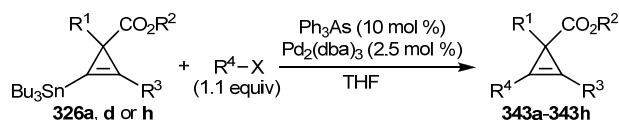
Tin–Iodine Exchange of Stannylcyclopropene 326d: Dimethyl 2-butyl-3-iodocycloprop-2-ene-1,1-dicarboxylate (342)



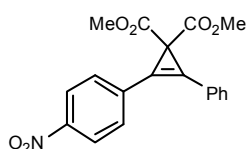
A solution of cyclopropene **326d** (50 mg, 0.10 mmol) and iodine (31 mg, 0.12 mmol) in Et₂O (0.5 mL) was stirred at room temperature for 20 h. The reaction mixture was filtered through a short plug of SiO₂ (*ca.* 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 20 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→25% EtOAc/hexane) gave the *iodocyclopropene* **342** (33 mg, 98%) as a colourless oil. IR (film) 2955, 2870, 1731 (C=O), 1435, 1281, 1247, 1147, 1063, 876, 741 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 3.73 (6H, s, 2 x OCH₃), 2.56 (2H, t, *J* = 7.3 Hz, =CCH₂), 1.64-1.58 (2H, m, =CCH₂CH₂), 1.44-1.37 (2H, m, CH₂CH₃), 0.93 (3H, t, *J* = 7.3 Hz, CH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 170.5 (2 x C), 124.5 (C), 52.3 (2 x CH₃), 44.2 (C), 36.9

(C), 27.7 (CH₂), 23.8 (CH₂), 22.2 (CH₂), 13.5 (CH₃); HRMS (ES) Exact mass calcd for C₁₁H₁₆IO₄ [M+H]⁺: 339.0088, found: 339.0089.

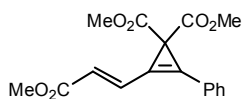
Stille Cross-Couplings of Stannylcyclopropenes: General Procedure E



A solution of Pd₂(dba)₃ (2.3 mg, 0.0025 mmol) and Ph₃As (3.1 mg, 0.01 mmol) in THF (0.5 mL) was stirred at room temperature for 15 min. A solution of the appropriate stannylcyclopropene (0.10 mmol) and the appropriate organohalide (0.11 mmol) in THF (0.5 mL + 0.5 mL rinse) was then added *via* cannula and the mixture was stirred at either 40 °C, 55 °C, or 60 °C until complete consumption of the stannylcyclopropene as observed by TLC analysis, or until no further reaction progress could be seen. The mixture was filtered through a short plug of SiO₂ (*ca.* 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/hexane) afforded the desired cyclopropene product.

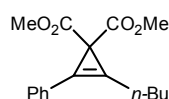


Dimethyl 2-(4-nitrophenyl)-3-phenylcycloprop-2-ene-1,1-dicarboxylate (343a).⁹² The title compound was prepared according to General Procedure E from **326a** (52 mg, 0.10 mmol) and 1-iodo-4-nitrobenzene (27 mg, 0.11 mmol) at a temperature of 40 °C for a reaction time of 20 h and purified by column chromatography (hexane→30% EtOAc/hexane) to give a yellow solid (32 mg, 91%) that displayed identical spectroscopic data to those reported previously.⁹²



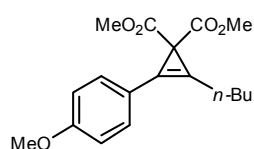
Dimethyl 2-[(E)-2-methoxycarbonylvinyl]-3-phenylcycloprop-2-ene-1,1-dicarboxylate (343b). The title compound was prepared according to General Procedure E from **326a** (52 mg, 0.10 mmol) and methyl (*E*)-3-iodoacrylate¹²² (23 mg, 0.11 mmol) at a temperature of 40

°C for a reaction time of 20 h and purified by column chromatography (hexane→30% EtOAc/hexane) to give a yellow solid (27 mg, 87%). m.p. 114-16 °C; IR (CHCl₃) 2953, 1723 (C=O), 1620, 1438, 1318, 1282, 1174, 1066, 910, 733 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.69-7.64 (2H, m, ArH), 7.63 (1H, d, *J* = 15.4 Hz, =CH), 7.50-7.45 (3H, m, ArH), 6.38 (1H, d, *J* = 15.4 Hz, =CH), 3.82 (3H, s, OCH₃), 3.74 (6H, s, 2 x OCH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 169.7 (2 x C), 166.2 (C), 131.2 (CH), 130.8 (2 x CH), 129.1 (2 x CH), 128.4 (CH), 126.4 (CH), 124.4 (C), 114.4 (C), 102.7 (C), 52.5 (2 x CH₃), 52.0 (CH₃), 34.5 (C); HRMS (ES) Exact mass calcd for C₁₇H₂₀NO₆ [M+NH₄]⁺: 334.1285, found: 334.1287.



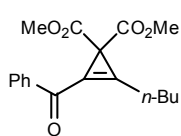
Dimethyl 2-butyl-3-phenylcycloprop-2-ene-1,1-dicarboxylate (343c).⁹² The title compound was prepared according to General

Procedure E from **326d** (50 mg, 0.10 mmol) and iodobenzene (13 μL, 0.11 mmol) at a temperature of 55 °C for a reaction time of 17 h and purified by column chromatography (hexane→30% EtOAc/hexane) to give a yellow oil (21 mg, 72%) that displayed identical spectroscopic data to those reported previously.⁹²



Dimethyl 2-butyl-3-(4-methoxyphenyl)cycloprop-2-ene-1,1-dicarboxylate (343d). The title compound was prepared

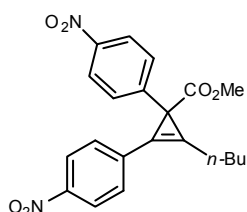
according to General Procedure E from **326d** (50 mg, 0.10 mmol) and 4-iodoanisole (26 mg, 0.11 mmol) at a temperature of 55 °C for a reaction time of 17 h and purified by column chromatography (hexane→30% EtOAc/hexane) to give a colourless oil (18 mg, 56%). IR (film) 2955, 2870, 1728 (C=O), 1605, 1509, 1436, 1250, 1173, 1062, 836 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.46 (2H, dm, *J* = 8.8 Hz, ArH), 6.94 (2H, dm, *J* = 8.8 Hz, ArH), 3.83 (3H, s, OCH₃), 3.71 (6H, s, 2 x OCH₃), 2.69 (2H, t, *J* = 7.4 Hz, =CCH₂), 1.76-1.70 (2H, m, =CCH₂CH₂), 1.49-1.42 (2H, m, CH₂CH₃), 0.96 (3H, t, *J* = 7.4 Hz, CH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 171.7 (2 x C), 160.4 (C), 131.1 (2 x CH), 117.5 (C), 114.3 (2 x CH), 106.4 (C), 103.7 (C), 55.4 (CH₃), 52.1 (2 x CH₃), 34.9 (C), 29.2 (CH₂), 24.1 (CH₂), 22.4 (CH₂), 13.7 (CH₃); HRMS (ES) Exact mass calcd for C₁₈H₂₃O₅ [M+H]⁺: 319.1540, found: 319.1538.



Dimethyl 2-benzoyl-3-butylcycloprop-2-ene-1,1-dicarboxylate

(343e). The title compound was prepared according to General Procedure E from **326d** (50 mg, 0.10 mmol) and benzoyl chloride

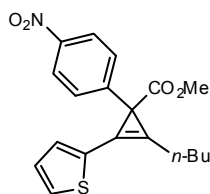
(13 μ L, 0.11 mmol) in THF at a temperature of 40 $^{\circ}$ C for a reaction time of 23 h and purified by column chromatography (hexane \rightarrow 30% EtOAc/hexane) to give a pale yellow oil (25 mg, 78%). IR (film) 2956, 2873, 1856 (C=O), 1736 (C=O), 1654, 1597, 1450, 1275, 1067, 703 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 8.08-8.06 (2H, m, ArH), 7.66-7.63 (1H, m, ArH), 7.55-7.52 (2H, m, ArH), 3.75 (6H, s, 2 x OCH_3), 2.85 (2H, t, J = 7.5 Hz, $=\text{CCH}_2$), 1.74-1.68 (2H, m, $=\text{CCH}_2\text{CH}_2$), 1.47-1.39 (2H, m, CH_2CH_3), 0.94 (3H, t, J = 7.4 Hz, CH_2CH_3); ^{13}C NMR (62.9 MHz, CDCl_3) δ 180.0 (C), 169.7 (2 x C), 136.4 (C), 134.1 (CH), 129.0 (2 x CH), 128.9 (2 x CH), 122.4 (C), 102.6 (C), 52.5 (2 x CH_3), 36.0 (C), 28.1 (CH_2), 25.1 (CH_2), 22.3 (CH_2), 13.6 (CH_3); HRMS (ES) Exact mass calcd for $\text{C}_{18}\text{H}_{21}\text{O}_5$ $[\text{M}+\text{H}]^+$: 317.1384, found: 317.1382.



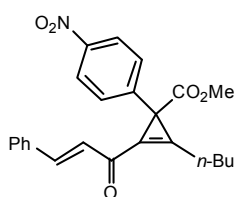
Methyl 2-butyl-1,3-bis-(4-nitrophenyl)cycloprop-2-enecarboxylate

(343f). The title compound was prepared according to General Procedure E from **326h** (56 mg, 0.10 mmol) and 1-iodo-4-nitrobenzene (27 mg, 0.11 mmol) at a temperature of 40 $^{\circ}$ C for a reaction time of 19 h and purified by

column chromatography (hexane \rightarrow 30% EtOAc/hexane) to give a yellow oil (39 mg, 99%). IR (film) 2957, 2872, 1722 (C=O), 1597, 1518, 1345, 1209, 1109, 856, 731 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 8.30 (2H, dm, J = 8.9 Hz, ArH), 8.14 (2H, dm, J = 8.9 Hz, ArH), 7.66 (2H, dm, J = 8.9 Hz, ArH), 7.51 (2H, dm, J = 8.9 Hz, ArH), 3.74 (3H, s, OCH_3), 2.83-2.79 (2H, m, $=\text{CCH}_2$), 1.79-1.70 (2H, m, $=\text{CCH}_2\text{CH}_2$), 1.49-1.38 (2H, m, CH_2CH_3), 0.95 (3H, t, J = 7.4 Hz, CH_2CH_3); ^{13}C NMR (62.9 MHz, CDCl_3) δ 173.0 (C), 147.8 (2 x C), 146.4 (C), 131.9 (C), 129.8 (2 x CH), 128.6 (2 x CH), 124.4 (2 x CH), 123.4 (2 x CH), 120.4 (C), 105.6 (C), 52.4 (CH_3), 35.5 (C), 29.3 (CH_2), 24.7 (CH_2), 22.4 (CH_2), 13.6 (CH_3); HRMS (EI) Exact mass calcd for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_6$ $[\text{M}]^+$: 396.1316, found: 396.1319.



Methyl 2-butyl-1-(4-nitrophenyl)-3-thiophen-2-yl-cycloprop-2-enecarboxylate (343g). The title compound was prepared according to General Procedure E from **326h** (56 mg, 0.10 mmol) and 2-iodothiophene (23 mg, 0.11 mmol) at a temperature of 60 °C for a reaction time of 17.5 h and purified by column chromatography (hexane→20% EtOAc/hexane) to give a yellow oil (22 mg, 61%). IR (film) 2951, 1720 (C=O), 1599, 1518, 1435, 1346, 1209, 1026, 852, 706 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.14 (2H, dm, *J* = 9.0 Hz, ArH), 7.56 (2H, dm, *J* = 9.0 Hz, ArH), 7.50 (1H, dd, *J* = 5.1, 1.1 Hz, CH), 7.19 (1H, dd, *J* = 3.6, 1.1 Hz, CH), 7.10 (1H, dd, *J* = 5.1, 3.6 Hz, CH), 3.73 (3H, s, OCH₃), 2.77-2.62 (2H, m, =CCH₂), 1.77-1.69 (2H, m, =CCH₂CH₂), 1.51-1.40 (2H, m, CH₂CH₃), 0.96 (3H, t, *J* = 7.4 Hz, CH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 173.4 (C), 148.7 (C), 146.3 (C), 129.3 (CH), 129.1 (CH), 128.9 (2 x CH), 128.4 (C), 127.9 (CH), 123.3 (2 x CH), 112.3 (C), 101.3 (C), 52.2 (CH₃), 36.4 (C), 29.3 (CH₂), 24.4 (CH₂), 22.5 (CH₂), 13.7 (CH₃); HRMS (ES) Exact mass calcd for C₁₉H₂₀O₄NS [M+H]⁺: 358.1108, found: 358.1108.

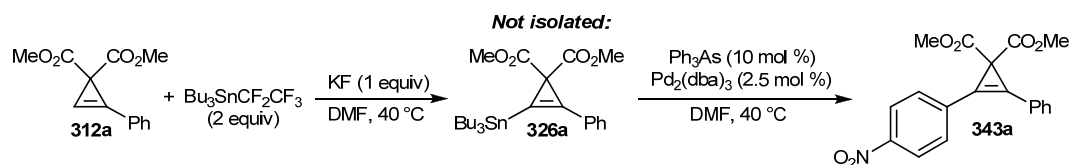


Methyl 2-butyl-1-(4-nitrophenyl)-3-[(E)-(3-phenylacryloyl)]cycloprop-2-enecarboxylate (343h). The title compound was prepared according to a slight modification of General Procedure E from **326h** (56 mg, 0.10 mmol) and

cinnamoyl chloride (25 mg, 0.15 mmol) at a temperature of 40 °C for a reaction time of 21 h and purified by column chromatography (hexane→30% EtOAc/hexane) to give a yellow oil (28 mg, 69%). IR (film) 2952, 1846 (C=O), 1724 (C=O), 1601, 1518, 1344, 1213, 1026, 858, 698 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.17 (2H, dm, *J* = 8.9 Hz, ArH), 7.79 (1H, d, *J* = 16.1 Hz, CH=CHC=O), 7.62-7.57 (4H, m, ArH), 7.47-7.42 (3H, m, ArH), 7.02 (1H, d, *J* = 16.1 Hz, =CHC=O), 3.74 (3H, m, OCH₃), 2.83 (2H, t, *J* = 7.4 Hz, =CCH₂), 1.76-1.68 (2H, m, =CCH₂CH₂), 1.48-1.36 (2H, m, CH₂CH₃), 0.93 (3H, t, *J* = 7.4 Hz, CH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 180.6 (C), 172.4 (C), 147.1 (C), 146.8 (C), 146.2 (CH), 133.9 (C), 131.3 (CH), 129.6 (2 x CH), 129.1 (2 x CH), 128.6 (2 x CH), 128.3 (C), 126.1 (CH), 123.5 (2 x CH), 106.8

(C), 52.6 (CH₃), 37.4 (C), 28.6 (CH₂), 25.6 (CH₂), 22.4 (CH₂), 13.6 (CH₃); HRMS (ES) Exact mass calcd for C₂₄H₂₄O₅N [M+H]⁺: 406.1649, found: 406.1650.

One-Pot Direct Stannylation–Stille Cross-Coupling: Synthesis of **343a**.⁹²



A solution of cyclopropene **312a** (23 mg, 0.10 mmol), KF (5.8 mg, 0.10 mmol) and Bu₃SnCF₂CF₃ (82 mg, 0.20 mmol) in DMF (0.4 mL) was stirred at 40 °C for 19.5 h. A solution of Pd₂(dba)₃ (2.3 mg, 0.0025 mmol), Ph₃As (3.1 mg, 0.01 mmol) and 1-iodo-4-nitrobenzene (27 mg, 0.11 mmol) in DMF (0.6 mL + 0.5 mL rinse) was then added *via* cannula. The resulting mixture was stirred at 40 °C for 21.5 h, cooled to room temperature, and then filtered through a short plug of SiO₂ (*ca.* 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→30% EtOAc/hexane) afforded the cyclopropene **343a** (23 mg, 66%) as a yellow solid that displayed identical spectroscopic data to those reported previously.⁹²

5. References

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